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Some Recent Studies and Investigations in Sterility

BY

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ALTHOUGH infertility is one of the oldest of human problems, it is only within the present century that real progress has been made in its study. But in these comparatively few years intensive work has been done in this subject and the accumulated literature is now enormous. It is not the intention here to refer to more than the essential relevant writings or to give an exhaustive account of a complete investigation of barren marriages. It is proposed, rather, to discuss certain selected aspects of the subject, viz. (I) the estimation of tubal patency, (II) anovular menstruation as assessed by endometrial biopsy, (III) endometrial tuberculosis, (IV) the causation of tubal occlusion, (V) seminal analysis, and (VI) the results obtained by a follow-up investigation. The observations which will be submitted are based on a consecutive and unselected series of 500 cases of primary sterility which have been followed up for several years and a number of more recent cases which have been the subject of particularized research.

It might indicate the general nature of the cases dealt with to state that in the series of 500 the duration of infertile marriage was as follows: Under 1 year, 4.6 per cent; 1 to 5 years, 64.4 per cent; 5 to 10 years, 26.8 per cent; over 10 years, 4.2 per cent. One might have expected a relatively higher incidence in the 5 to 10 years' group, but it is a common clinical observation that a large number of couples seem to reconcile themselves to infertility and do not seek medical advice on this point when their marriage has proved infertile after 5 years. The age incidence of the female partners at the time of study showed no features of note, about two-thirds of them being in the 20 to 30 age group.

(I) THE ESTIMATION OF TUBAL PATENCY.

The methods employed have been (A) insufflation and (B) hysterosalpingography.

A. *Insufflation.*

The total number of patients in the series, whose tubes were insufflated, amount to 480, of whom 232 had two or more insufflations. In most instances the test was repeated simply as a confirmatory procedure: in many it was done to compare the findings with and without anaesthesia; but in 22 patients 6 or more insufflations were done to study the behaviour of tubes over a considerable period of time. The figures in this group are as follows:

6	insufflations	were	performed	in	11	cases
7	,,	,,	,,	,,	4	,,
8	,,	,,	,,	,,	2	,,
9	,,	,,	,,	,,	1	case
9	,,	,,	,,	,,	1	,,
12	,,	,,	,,	,,	1	,,
14	,,	,,	,,	,,	1	,,
23	,,	,,	,,	,,	1	,,
25	,,	,,	,,	,,	1	,,

The total number of insufflations performed in the whole series is 1,003. The tubal status of the 480 patients of the series is briefly summarized, viz.:

	Number of patients	Percentage
Normal patency	283	58.9
Non-patency	182	38.0
Spasm-normal patency ...	12	2.5
Peritubal adhesions and tubal strictures ...	3	0.6

Since March, 1937, the kymograph has been used in conjunction with tubal insufflation and it may here be stressed that its value cannot be over-estimated. The kymograph has been used in approximately 75 per cent of the above cases. Fig. 1 illustrates the instrument as made by Messrs. Kelvin, Bottomley and Baird. This is the most recent apparatus manufactured and it incorporates the main features first devised by Rubin and subsequently modified by Bonnet.

Further consideration may now be given to the features of note in each of these groups, but it will be more convenient to consider them in the following order, (1) normal patency, (2) spasm-normal patency, (3) peritubal adhesions and tubal strictures, and (4) non-patency.

(1) *Normal Patency*. In 75 per cent of these 283 cases gas passed through the tubes at a pressure below 120 mm. Hg. Patency below 50 mm. Hg. or above 170 mm. Hg. was uncommon and was found in not more than 5 per cent of the total.

(2) *Spasm-normal Patency*. There were 12 patients in this category. Three features of importance emerge from a study of this group: (*a*) Cases of tubal spasm may show on occasion apparent non-patency at 200 mm. Hg. (high degree of spasm). (*b*) Similarly, these cases may show occasional normal patency without spasm, and (*c*) The condition does not seem to be an important factor in causing infertility since 5 of the 12 cases became pregnant (the husband of one of the remainder showed complete azoospermia).

(3) *Peritubal Adhesions and Tubal Strictures*. Although a number of cases showed minor degrees of tubal stenosis as evidenced by patency at high pressure and/or absence or gross diminution of peristaltic waves, only 3 showed noteworthy degrees of this condition.

(4) *Non-Patency*. The pattern of the tracing obtained in complete tubal blockage is obvious (Fig. 2), but the following circumstances cast doubt on the validity of a single finding of this typical tracing as being diagnostic of blockage: (*a*) some patients became pregnant after tubal insufflation had demonstrated apparent non-patency, (*b*) as already indicated, some cases of tubal spasm showed on occasion apparent non-patency at 200 mm. Hg. and (*c*) in the course of these studies 25 cases were encountered in whom an apparent non-patency was found on occasion in tubes which at other times were proved to be permeable.

These findings suggested the need for fuller investigation of possible fallacies, that is, the effect of variation in the rate of flow of the gas, the time-relationship of insufflation to the phase of the cycle (particularly the premenstruum), and the effect of anaesthesia. It was considered desirable to study, firstly, the effect of these factors, by repeated insufflation, on tubes which were known to be patent.

Numerous experimental insufflations, therefore, were carried out in both anaesthetized and non-anaesthetized patients to determine whether variations in the rate of flow of gas into patent tubes could materially alter the appearance of a kymo-

graphic tracing, even to the extent of simulating tubal blockage. Numerous variations from 30 c.c. per minute to 120 c.c. per minute (the latter rate is never used in clinical routine) were employed and in varying sequences, i.e. in some cases the rate of flow was progressively increased: in others the initial high rate was progressively decreased (Fig. 3). In a few instances the excessive rate of flow of the gas caused the pressure to rise considerably, but never above 150 mm. Hg.: and in no case was the tracing of non-patency obtained. In these instances the findings appeared to bear no relationship to the phase of the cycle. It was concluded that, although increase in the rate of flow of the gas may be followed by marked increase in the patency-pressure level with more active, deeper peristaltic waves, this finding is not invariable and, at all events, the general appearance of the kymographic tracing is not materially altered.

It was considered that further knowledge of tubal patency and kymographic function could best be obtained by repeated insufflations over long periods of time. For this purpose 9 patients showing normal tubal patency were insufflated on 6 or more occasions. One of them was insufflated 23 times and another 25: fuller details of these 2 cases may now be given.

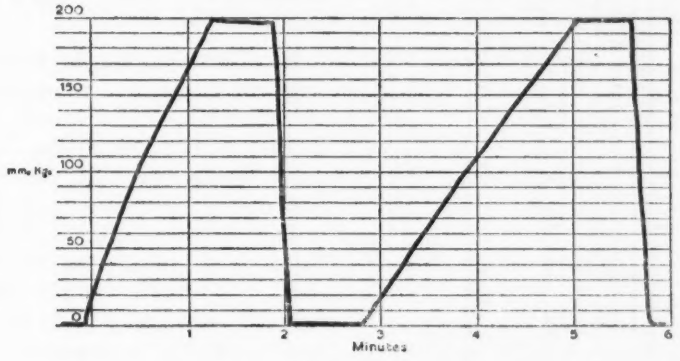


FIG. 2.

Kymographic tracing in tubal occlusion. Pressure rises 200 mm. Hg. and is maintained at this level by the operator preventing further flow of gas. The pressure falls abruptly as soon as the gas is allowed to escape.

First Patient. Twenty-three kymographic insufflations at a constant rate of flow (30 c.c. per minute) were performed without anaesthesia between May 19th, 1939, and December 28th, 1939. They fall into 3 groups, viz.:

1. Two in May, 1939.
2. Twelve in June and July, 1939.
3. Nine in December, 1939.

The complete set of tracings is illustrated (Fig 4). The 2 insufflations performed in May were simply diagnostic and routine. During the tests, however, it was apparent that the patient was a very suitable subject psychologically and physically for a contemplated study of tubal behaviour by means of frequent insufflations throughout a menstrual cycle. She was asked to report on the day after her next menstruation concluded.

The first insufflation of the series, performed in June and July, was on June 15th 1939, and the test was repeated every alternate day until July 16th, 1939, with two

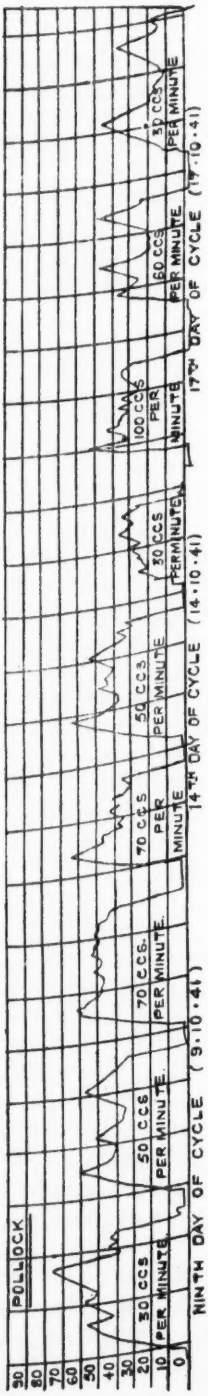


FIG. 3.
Kymographic tubal insufflation. Tracings illustrate the effect of alteration in the rate of flow of the gas.

exceptions—domestic reasons prevented her attending on June 25th, 1939, and also on July 9th, 1939, but the latter omission is compensated for by an insufflation on the following day, which was 2 days prior to menstruation.

In all but 2 instances the tracings show frequent and active tubal peristalsis with patency and waves within the pressure limits of 50 and 80 mm. Hg. The exceptions occur on the twentieth and twenty-second day of the cycle when patency is shown around 120 mm. Hg. and the tubal contractions are infrequent and of low amplitude. Six months later it was decided to repeat a series as a basis for comparison. Unfortunately, the patient was unable to attend as arranged and only 9 tests were performed before menstruation intervened. In this group, too, patency was established usually between pressures of 50 and 80 mm. Hg. with active peristaltic waves. More detailed comparison of both series, however, does not show any noteworthy cyclical correspondence.

Second Patient. Twenty-five kymographic insufflations at a constant rate of flow were performed with anaesthesia between March 4th, 1940 and October 17th, 1941. After the first test the patient was asked to report on the day following her menstrual period. Thereupon a series was commenced on April 4th, 1940, and an insufflation was done *every day* until May 9th, 1940, on the evening of which day menstruation recurred. (Fig. 5 illustrates these 18 results in a daily investigation of tubal behaviour in a complete menstrual cycle). This, as far as can be ascertained from a study of the literature and a personal communication from Rubin (December 20th, 1941) is the first occasion on which daily insufflation has been performed throughout the cycle.

The similarity of most of the tracings at different points in the cycle is striking and

FIG. 4.
Kymographic tubal insufflation performed: (1) Twice

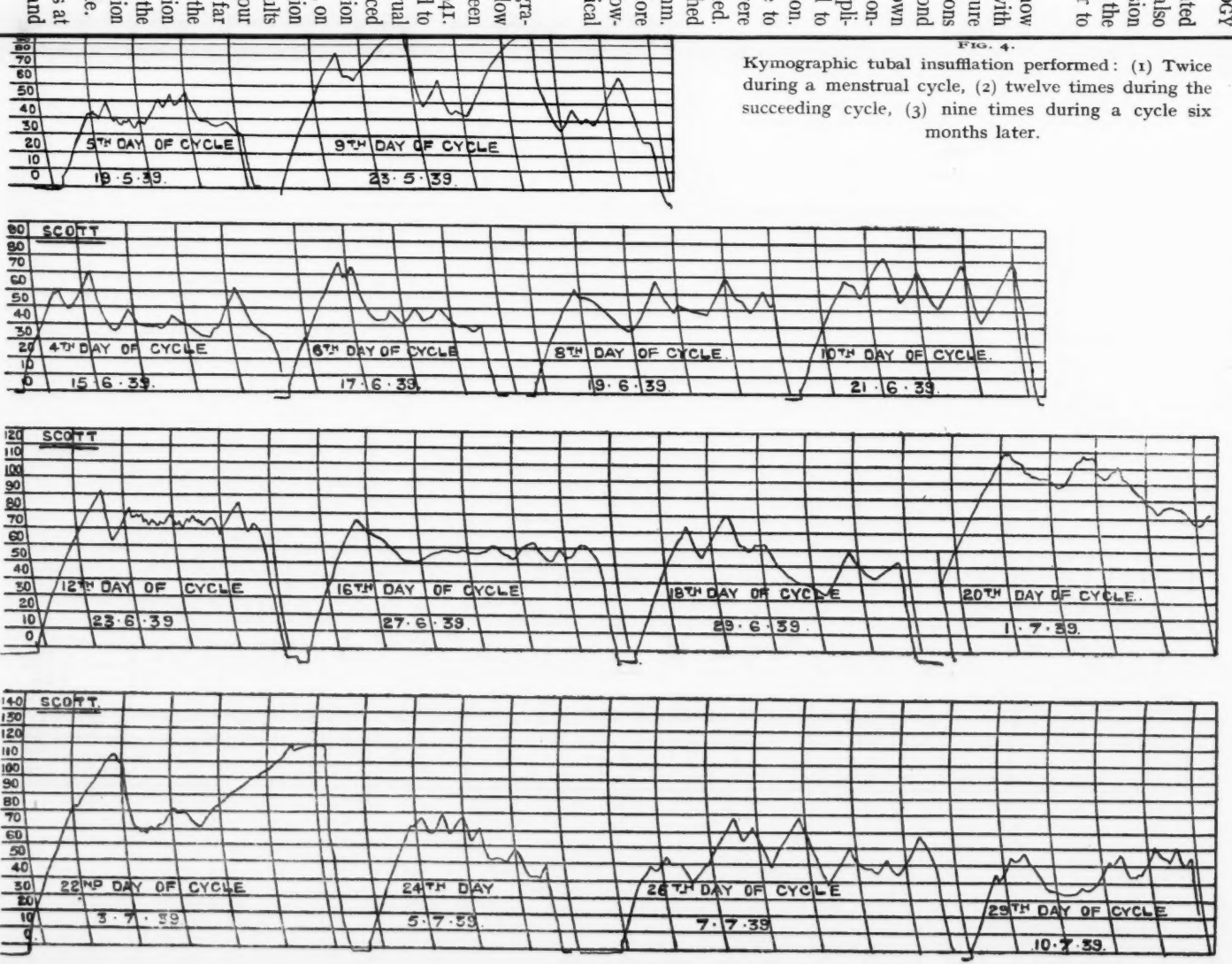
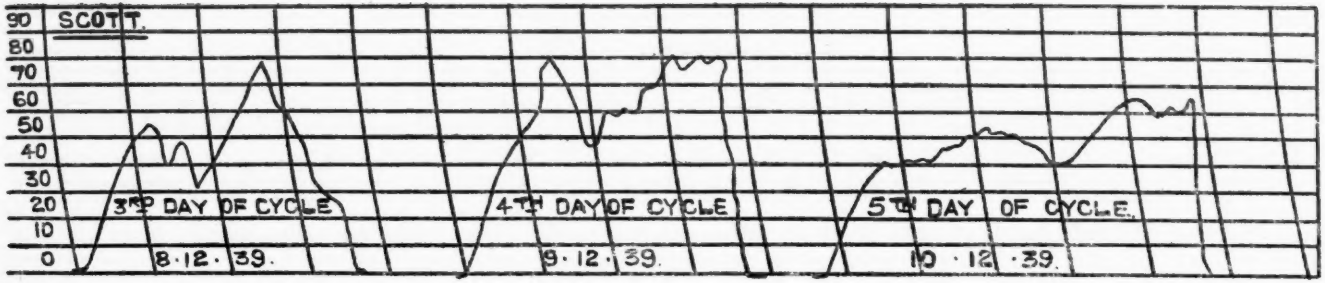


FIG. 4.

Kymographic tubal insufflation performed: (1) Twice during a menstrual cycle, (2) twelve times during the succeeding cycle, (3) nine times during a cycle six months later.


90
80
70
60
50
40
30
20
10
0
SCOTT.
3RD DAY OF CYCLE
8·12·39.
4TH DAY OF CYCLE
9·12·39.
5TH DAY OF CYCLE.
10·12·39.

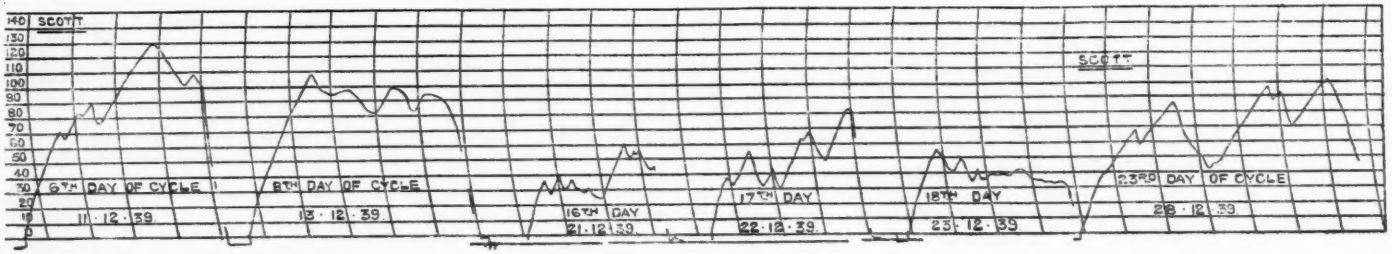

140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
SCOTT
6TH DAY OF CYCLE
11·12·39
8TH DAY OF CYCLE
13·12·39
16TH DAY
21·12·39
17TH DAY
22·12·39
18TH DAY
23·12·39
SCOTT
23RD DAY OF CYCLE
28·12·39

FIG. 4(*a*).

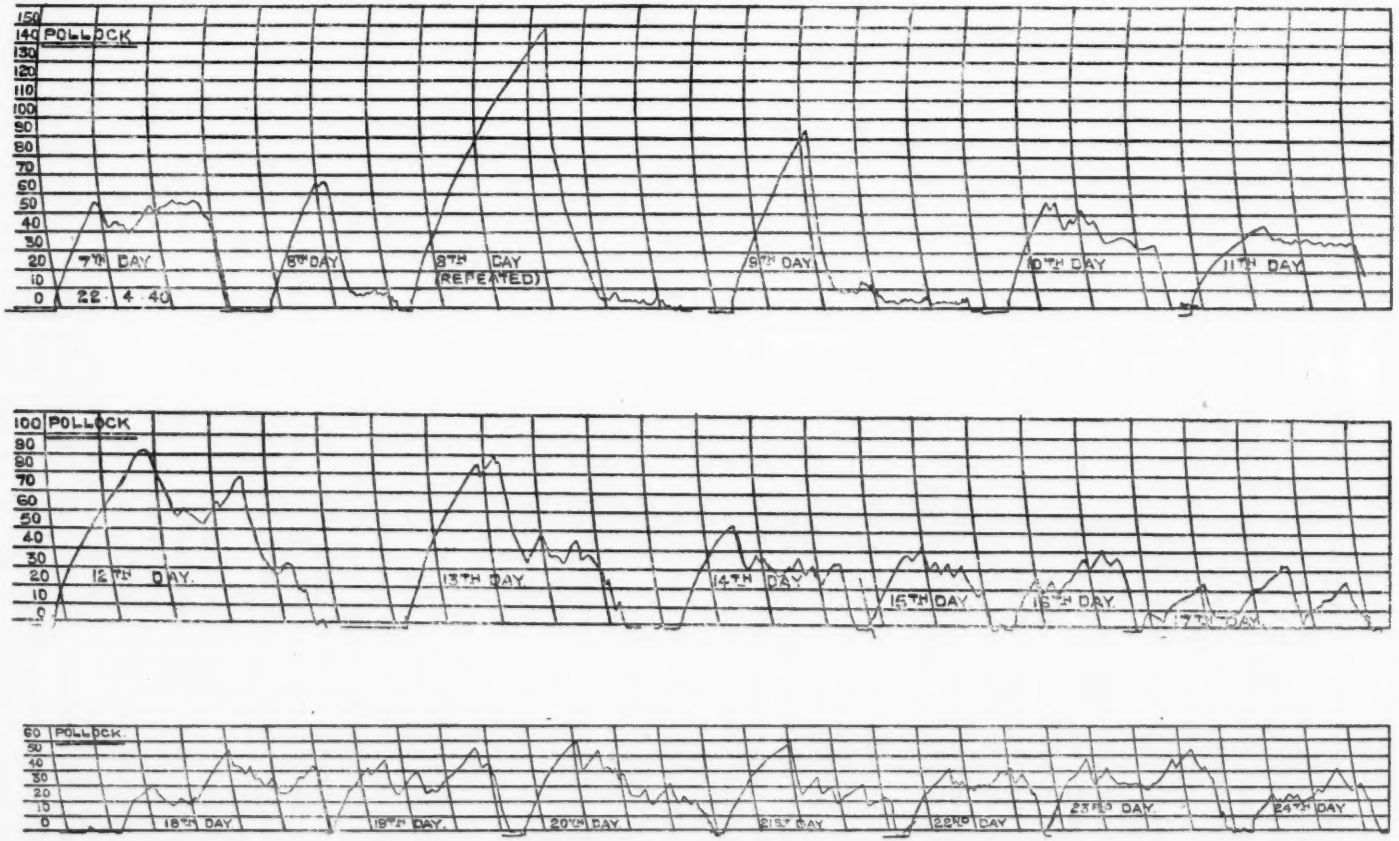


FIG. 5.

Kymographic tubal insufflation performed on every day of a complete menstrual cycle (24 days).

gives little indication that their appearance is influenced by or correlated to phases of endometrial or ovarian activity. A marked degree of spasm, followed by numerous waves at very low pressure is shown in the tracings of the eighth day, the ninth day, and in a less typical form on the twelfth and thirteenth day.

The results of these repeated insufflations (9 cases) may be summarized as follows:

(1) No great difference, either in the level at which patency is established or in the appearance of tubal contraction waves, is usually seen in any given patient when insufflation is repeated, even after several months.

(2) Around ovulation-time (presumptive) more active or more frequent peristalsis may be seen. This also is not invariable and there is no indication that there is any constant close correspondence between the type of tracing obtained (tubal patency and peristalsis) and the stage of the endometrial cycle. It must be admitted that this is not in agreement with Rubin's findings (1939) but nevertheless corroborative information was obtained in these points by the following further observations.

A study of the group of 25 patients with patent tubes, but who showed on one insufflation apparent non-patency, revealed that the latter findings occurred irregularly in the cycle and were not related to any particular phase. Moreover, in a patient in whom kymographic insufflation was performed on 20 consecutive days (menstruation intervening), no material change in the type of tracing occurred at any phase: all showed patency.

The effect of anaesthesia on tubal patency and on apparent blockage, as recorded by kymographic insufflation, was studied in 6 cases. Various anaesthetics were employed, viz., gas-oxygen, ether, chloroform, and intravenous evipan sodium. In 3 of the cases insufflation was performed firstly *without* and immediately thereafter *with* anaesthesia; in the other 3 it was done firstly under anaesthesia and soon after the anaesthetic had been discontinued. No anaesthetic had any material effect on the type of tracing obtained (Fig. 6).

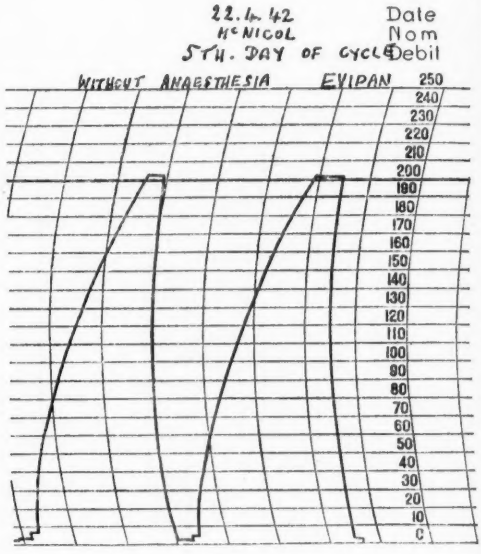


FIG. 6.
Kymographic tubal insufflation: the effect of anaesthesia on the type of tracing obtained.

More detailed consideration may now be given to the fallacious diagnosis of non-patency as the result of a single insufflation. This problem is approached from three aspects, viz. (1) a study of the group of 25 cases, already referred to, in whom an apparent non-patency was found on occasion in tubes which at other times showed normal patency, (2) comparison with hysterosalpingography and (3) the incidence of pregnancy. The findings may be summarized as follows: (1) In 9 patients 2 tests only were performed; in 15 patients 3 tests, 2 showing patency and 1 non-patency. In one patient 4 tests, 3 showing patency and 1 non-patency. Thus, none of the patency

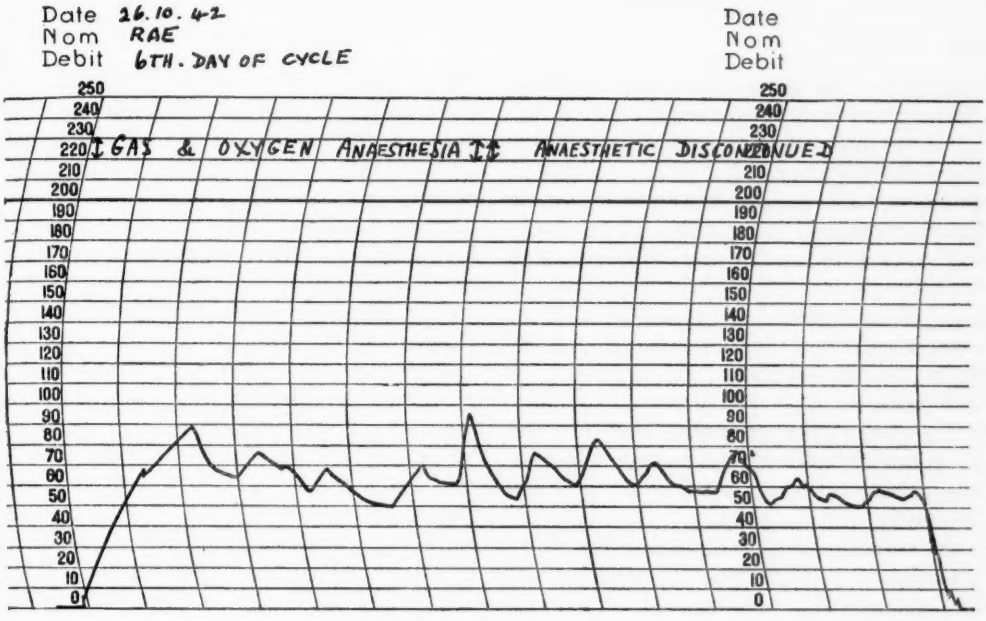


FIG. 6 (*a*)

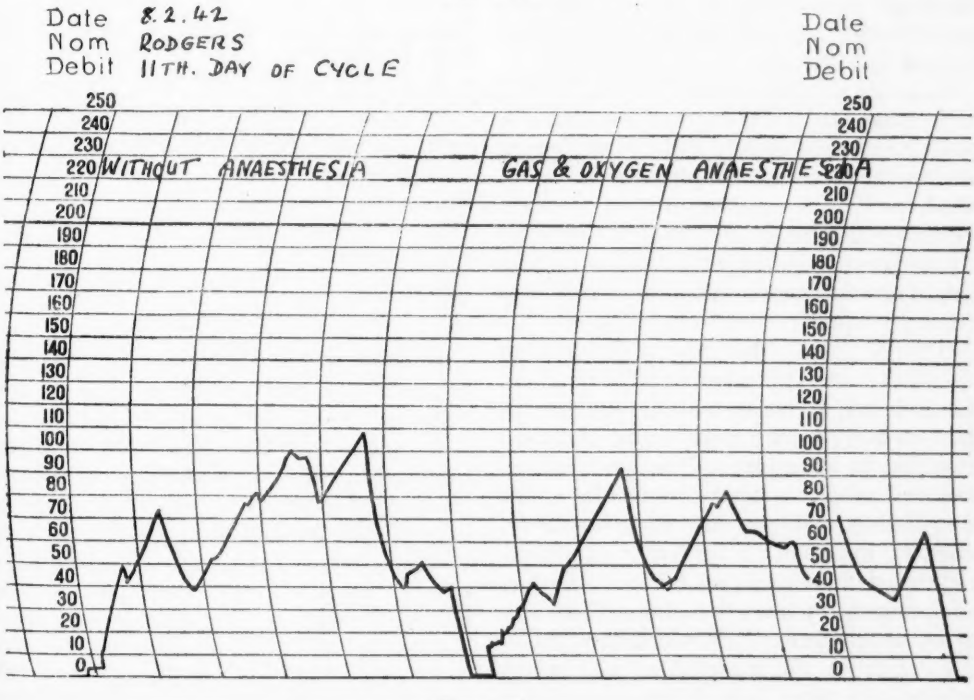


FIG. 6 (*b*)

Kymographic tubal insufflation: the effect of anaesthesia on the type of tracing obtained.

cases showed non-patency more than once. Anaesthesia was employed in 12 of the group on the occasion on which insufflation showed non-patency. In 2 of the remainder, patency was shown under anaesthesia but non-patency without it. The remaining cases (11) had no anaesthetic at any insufflation.

(2) In a series of 60 cases, subsequent examination by lipiodol showed that insufflation had erroneously indicated blockage in 6 cases.

(3) Among 116 patients who became pregnant 29 had been diagnosed as having non-patent tubes as a result of a single insufflation.

An additional group of 4 cases, in whom a finding of patency was followed by 1 of non-patency on a subsequent date, showed the "non-patency" finding at the premenstrual phase in 1 only, in the remainder insufflation having been performed in the first half of the cycle.

It would appear therefore that, although it is generally held, for various reasons, that insufflation should not be performed during the premenstrual phase of the cycle, the hypothetical consideration that the temporary thickening of the endometrium around the uterine end of the Fallopian tube might give an erroneous finding of blockage finds no support in our observations.

The conclusions that may be drawn from the above are (1) in cases of tubal patency, an isolated or occasional finding of apparent non-patency may occur and this, equally, in anaesthetized and non-anaesthetized subjects, (2) the result of a single insufflation, with or without anaesthesia, showing apparent non-patency, cannot be depended upon, and (3) a fallacious finding of non-patency may be obtained at any point of the cycle. It would follow, therefore, that in all reported series, except where 2 or more insufflations (and/or a hysterosalpingogram) established non-patency, dependency on a single finding of non-patency has given too high an incidence in the past.* It has been suggested that a finding of patency subsequent to one of non-patency may be explained by the therapeutic effect of the first test. This view finds no substantiation in our results since if non-patency were found on 2 or more occasions, no success in restoring patency was achieved by repeated insufflation.

To sum up, these investigations have had a negative result in that no light has been thrown on the causation of "pseudo-blockage," but they prove that the above-mentioned factors are not responsible. Assuming no blockage in the instrument employed for insufflation (which should be tested both before and after use), tubal or utero-tubal spasm, for no apparent reason, on occasion resists the pressure of gas up to 200 mm. Hg. This spasm is sometimes very apparent in hysterograms and may be illustrated on occasion in kymographic tracings, when repetition of insufflation a few seconds later shows gas passing through tubes after initial failures. Repeated insufflations have also shown that spasm, whether of lesser or major degree, is not a constant state and that many tracings may show normal patency (Fig. 7).

B. *Hysterosalpingography.*

Lipiodol was injected into the uterus and tubes and radiographs then taken in 114 patients on whom 1 or more insufflations had already been performed; in 15 of them a further lipiodol examination was made at an interval (varying from several weeks to several months) and in 1 case the test was

* My own figure of 38 per cent non-patent, when corrected by the results of hysterosalpingograms and the incidence of pregnancy is reduced to barely 30 per cent. Moreover, since the completion of the above series a consecutive and unselected series of 563 primary sterility cases has shown an incidence of non-patency of 26.8 per cent.

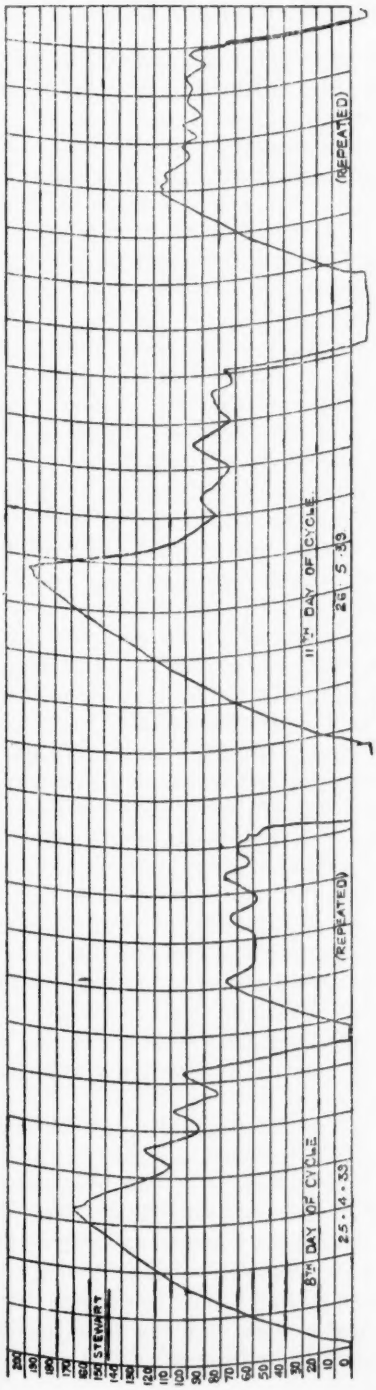


FIG. 7.

Kymographic tubal insufflation to illustrate marked tubal spasm and the effect of immediate repetition of the test.

performed on 3 occasions with an interval of 3 weeks between the first and second, and 4 months between the second and third. Thus, in all, 131 lipiodol injections were made. In every instance an X-ray photograph of the pelvis was taken immediately after lipiodol injection and another either 24 or 48 hours later.

Complications were uncommon and similar to those observed during and immediately after tubal insufflation, much the most frequent being momentary faintness. Their general incidence was a little higher than on insufflation and the complaint of abdominal or pelvic pain during the injection was definitely more frequent. On a few occasions the pain was sufficient to make the completion of the test unsatisfactory or impossible and this accounts for some of the 'unsatisfactory' findings in the analysis of results. Before these are described, brief reference may be made to 2 sequelae, (1) in one patient, lipiodol appeared to have entered uterine veins; this, at any rate, is suggested by the appearance in the X-ray films: fortunately this caused no upset whatever: and (2) 1 patient developed pelvic sepsis.

The results in the series of 114 cases were as follows:

Bilateral tubal patency was revealed in	59 cases
Unilateral patency was revealed in ...	7 ,,
Non-patency was revealed in	40 ,,
The test proved unsatisfactory in	8 cases.

Further study of the non-patent group shows, firstly, that it formed 37.7 per cent of the total (comparing very closely with the figure of 38.0 per cent arrived at by insufflation in 480 patients, already described) and, secondly, that the blockage appeared to be at the fimbriated ends in 22 cases, at the uterine ends in 13, and at one end of one tube and the other end of the other in 5 cases.

Comparison of insufflation results with those of lipiodol shows that patency demon-

strated by insufflation was confirmed by lipiodol in 54 of the 60 cases. The discrepancy in the remaining 6 cases, which showed tubal patency with lipiodol but non-patency with insufflation, merits further consideration. In each instance only one insufflation had been performed, anaesthesia having been employed on 3 occasions; the evidence of the passage of lipiodol through the tubes seems incontrovertible; 3 of the 6 cases became pregnant (18 months, 6 months, and 48 months later respectively). Unless one assumes a patency-establishing effect of a single insufflation in each of these cases, the only conclusion appears to be that the lipiodol results were correct and the insufflation ones were not. Thus, hysterosalpingography has demonstrated an erroneous insufflation-finding of non-patency in 6 of a group of 60 cases (10 per cent). This finding confirms the view expressed earlier, in considering the results of repeated insufflations, namely, that reliance cannot be placed upon a single insufflation finding of non-patency.

Further comparison of the results shows that in all 7 cases showing unilateral patency with lipiodol, insufflation gave evidence also of patency, in one case at high pressure-level and exhibiting spasm. Too much reliance, however, should not be placed on the radiological appearance of unilateral patency, since the apparent failure of lipiodol to enter a tube or pass through it may be due to insufficiency either in the amount of lipiodol or its pressure. This possibility is illustrated in reviewing those cases which erroneously showed apparent non-patency with lipiodol and also in several of the patients who had hysterographs repeated.

Of the 40 cases showing non-patency after lipiodol, 36 had given the same result on insufflation. The remainder showed definite patency on insufflation, performed once in 1 case (Jennings, Case 418), twice in another (Buchanan, Case 318), and on 6 occasions in the remaining 2 (Brophy, Case 204, and Gilchrist, Case 242). Case 318 became pregnant 1 month after her second insufflation (or 2 months after lipiodol). There is no doubt in these cases radiographs gave erroneous evidence of tubal blockage. In each instance radiographs taken 24 hours after lipiodol injection showed no evidence of lipiodol "spill" through the tubes.

Further critical evaluation of hysterosalpingography is obtained from a study of a group of cases in which this mode of investigation of the tubal status was repeated subsequently in the same patient. It has already been mentioned that the test was done twice in 15 patients and thrice in 1 (Fig. 8). Of these 16 cases, in 1, both results were quite unsatisfactory and in another sufficiently poor to render their accurate assessment impossible. In the remaining 14 cases, 7 showed a notable discrepancy in the appearances of the respective radiographs. In 2 of the others (Buchanan, Case 318, and Ross, Case 278) the second lipiodol injection was inadvertently made while the patient was in the first few weeks of pregnancy, i.e. before she had missed a 'period', fortunately without disturbance to gestation: in one of them both radiographs showed tubal patency and in the other both showed bilateral isthmial blockage. In 4 cases where repetition of lipiodol injection at varying intervals showed variations in the appearances obtained the diagnosis of patency or non-patency was corroborated.

From the above considerations one important conclusion may be drawn, namely, that accurate interpretation of a hysterosalpingograph may often be difficult. Thus, it may show blockage where none exists or its interpretation may be so difficult that an accurate conclusion cannot be reached. But it may show definite patency when insufflation has indicated blockage and in non-

patent tubes it will reveal the precise site of blockage.

(II) Anovular Menstruation as Assessed by Endometrial Biopsy.

It is generally agreed that the presence of secretory changes in the endometrium is *reliable* evidence of corpus luteum activity and *presumptive* evidence of ovulation. Novak (1940) declares: "For the present it still seems justified to assume that ovulation has occurred if the endometrium just before menstruation reveals a full-blown progestational type of endometrium and that the finding of a purely proliferative endometrium or one showing slight or uncertain evidences of secretory activity at a chronologically premenstrual phase, is justifiable presumptive evidence that ovulation has not occurred."

In the initial series of 500 cases, 850 endometrial biopsies were performed, by far the larger percentage of them by means of Sharman and Sheehan's biopsy curette in the unanaesthetized patient. In the remainder, either curettage under anaesthesia, or suction (in the early cases of the series) without anaesthesia was employed. Endometrium was removed and examined in 392 cases of the initial series of 500. Unfortunately, not all of them had endometrium removed at the premenstrual phase of the cycle, mainly because, in the early cases, the significance of biopsy, at this specific phase, in relation to ovulation was not adequately appreciated or because of difficulty in timing biopsy in those with irregular menses, or because of the patient's failure to report after tubal insufflation, or because she could not be traced. However, in 358 cases endometrium was removed in the premenstrual phase of the cycle. Of these, 335 showed the normal characteristic, secretory or differentiative features of this phase; 11 showed absence of these features at this phase on one or more occasion, but not on all; and 12 showed their absence on every occasion on which biopsy was performed.

It is not proposed to discuss further these 335 cases which showed the normal endometrial appearances of the premenstrual (or postovulatory) stage, but detailed consideration may now be given to the group of 23 cases exhibiting definitely anovular cycles in the series of 358 (6.4 per cent). It is proposed to describe them in two sections: A, those exhibiting both 'anovulatory' and 'secretory' cycles in the same patient—to be described as the "periodically anovular series," and B, "constantly anovular series." It must be appreciated that these titles are being used descriptively and as a matter of convenience and cannot be expected to refer to more than the relatively small period of time during which the patients were studied. The two series therefore are not mutually exclusive since cases in Section A might at any future time show, during a certain period of observation, features of section B and, alternatively, cases in section B might possibly at one examination or another show 'secretory' endometrium. Moreover, many of the series of 335 patients already described as showing normal secretory characters, might, if the duration of their study were prolonged, show at one time or another apparently anovular cycles.

A. Periodically Anovular Series (11 cases).

Beveridge, Case No. 183.

1. 20/4/37, anovular, 3 days premenstrual
2. 7/3/38, anovular, 5 days premenstrual
3. 11/4/38, secretory, 1 day premenstrual
4. 11/5/38, secretory, 4 days premenstrual

Ferguson, Case No. 313.

1. 8/9/38, anovular, 2 days premenstrual
2. 7/11/38, secretory, 2 days premensttrual
3. 7/12/38, secretory, 2 days premenstrual
4. 8/3/39, anovular, 1 day premenstrual

Forrest, Case No. 338.

1. 30/11/38, anovular, 1 day premenstrual
2. 25/1/39, anovular, 6 days premenstrual
3. 27/3/39, secretory, 4 days premenstrual
4. 25/5/39, secretory, 8 days premenstrual

In the last of the above instances menstruation was 6 days later than expected.

Garth, Case No. 324.

1. 21/11/38, anovular, 2 days premenstrual
2. 11/5/39, secretory, 1 day premenstrual
3. 11/5/39, secretory, 2 days premenstrual
4. 10/2/41, secretory, 2 days premenstrual

Karnouskie, Case No. 364.

1. 13/3/39, anovular, 1 day premenstrual
2. 12/4/39, secretory, 4 days premenstrual
3. 12/5/39, anovular, 8 days premenstrual
4. 19/6/39, secretory, 3 days premenstrual
5. 30/11/39, secretory, 5 days premenstrual

The significance of No. 3 in this case might be questioned since menstruation occurred 8 days after biopsy, although due in 4 days, but the appearances do not correspond with the date in the cycle.

Kennedy, Case No. 445.

1. 20/11/39, secretory, 2 days premenstrual
2. 27/4/40, anovular, 4 days premenstrual

Martin, Case No. 132.

1. 5/5/39, secretory, 3 days premenstrual
2. 6/6/39, anovular, same day as menstruation
3. 3/7/39, secretory, 3 days premenstrual

McCabe, Case No. 339.

1. 26/10/38, anovular, 5 days premenstrual
2. 13/1/39, secretory, 6 days premenstrual
3. 13/2/39, anovular, 3 days premenstrual

McInnes, Case No. 325.

1. 26/10/38, secretory, 2 days premenstrual
2. 28/11/38, anovular(?),8 days premenstrual
3. 30/1/39, secretory, 4 days premenstrual
4. 7/6/39, anovular, 6 days premenstrual
5. 16/11/42, secretory, 3 days premenstrual

In No. 2 menstruation was 2 days overdue.

Simpson, Case No. 271.

1. 4/3/38, anovular, 4 days premenstrual
2. 25/4/38, secretory, 3 days premenstrual
3. 20/5/38, anovular, 3 days premenstrual

White, Case No. 323.

1. 10/11/38, secretory, 1 day premenstrual
2. 5/12/38, anovular, 2 days premenstrual
3. 21/6/39, anovular, 3 days premenstrual

B. "Constantly" Anovular Series. (12 cases).

In 3 of the following cases biopsy was not repeated and so, although the endometrium was of the anovular type, the term "constantly" is not strictly appropriate.

Carlin, Case No. 186.

1. 26/3/37, anovular, 3 days premenstrual
2. 1/7/38, anovular, 4 days premenstrual
3. 31/7/41, anovular, 2 days premenstrual

Craig, Case No. 227.

1. 20/11/37, anovular, 2 days premenstrual

Graham, Case No. 111.

1. 30/1/36, anovular, 1 day premenstrual

Four subsequent premenstrual biopsies were attempted on the following dates (1) October 21st, 1937; (2) November 18th, 1937; (3) September 1st, 1938; and (4) November 4th, 1941. In none of them was any endometrium obtained: only mucoid material and amorphous debris.

Hirstfield, Case No. 179.

1. 21/4/37, anovular, 3 days premenstrual
2. 18/5/37, anovular, 3 days premenstrual
3. 29/9/37, anovular, 7 days premenstrual

Logan, Case No. 125.

1. 23/4/36, anovular, 1 day premenstrual
2. 25/5/36, anovular, 6 days premenstrual
3. 23/11/36, anovular, 5 days premenstrual
4. 23/2/37, anovular, 1 day premenstrual
5. 27/3/37, anovular, same day as menstruation.
6. 22/4/37, anovular, 2 days premenstrual

Lyttle, Case No. 459.

1. 21/12/39, anovular, 3 days premenstrual
2. 4/3/40, anovular, 1 day premenstrual
3. 28/3/40, anovular, 3 days premenstrual

Maloney, Case No. 261.

1. 9/11/38, anovular, 3 days premenstrual
2. 7/12/38, anovular, 2 days premenstrual
3. 1/2/39, anovular, 2 days premenstrual

McKenzie, Case No. 268.

1. 4/4/38, anovular, 2 days premenstrual
2. 24/6/38, anovular, 1 day premenstrual

McVean, Case No. 372.

1. 22/3/39, anovular, 3 days premenstrual
2. 10/2/41, anovular, 2 days premenstrual
3. 3/3/41, anovular, 3 days premenstrual
4. 15/5/41, anovular, 1 day premenstrual

Sherlock, Case No. 454.

1. 23/9/41, anovular, 2 days premenstrual

Sim, Case No. 363.

1. 2/3/39, anovular, 2 days premenstrual

Stronach, Case No. 387.

1. 22/6/39, anovular, 2 days premenstrual
2. 23/10/41, anovular, 1 day premenstrual
3. 27/11/41, anovular, 4 days premenstrual
4. 26/1/42, anovular, 2 days premenstrual

It must be emphasized that an erroneous diagnosis of anovular cycles may be made if reliance is wholly placed on the date of the *preceding* menstruation and biopsy is performed only in the presumptive premenstrual phase. The date of menstruation after *biopsy* must be ascertained.

Two further observations must be made: (1) Although it is a simple matter to distinguish an early proliferative from a late differentiative endometrium, it is very difficult in some cases to decide whether an endometrium is in the late proliferative or early secretory phase, since the one merges into the other, and (2) a second potential source of error is that the observer is dependent very frequently on the patient correctly noting or accurately remembering the date of menstruation.

It may be observed at this point that none of these 23 patients became pregnant during the period of study and that only two did so under treatment. This is not surprising in view of the serious nature of the dysfunction. Anovular menstruation is therefore a major infertility factor when it occurs, although its actual incidence is low.

(III) Recent Observations on Endometrial Tuberculosis.

The examination of endometrium in 392 of the original series of 500 cases showed unsuspected tuberculosis in 20 (5.1 per cent). Since the completion of that series a further 491 consecutive and unselected cases of primary sterility have had endometrium examined and of these 27 have shown tuberculosis (5.5 per cent). This gives a total incidence of 5.3 per cent in 883 cases.

In the first instance this finding of unsuspected tuberculosis was largely an accidental discovery in endometrium removed primarily with a view to the diagnosis of anovulation. In this part of the investigation I worked in close association with A. M. Sutherland, who subsequently extended his observations to cases other than those of sterility. The histological characters of the lesion and the proofs of its tuberculous nature have been fully discussed by Sutherland (1943). All but one of the cases in my series are incorporated in his paper and it is therefore unnecessary to discuss the pathological aspects here.

Microphotographs of endometrium from several representative cases are shown in Plates I, II and III. The following are the details of the biopsies and findings in each case of the original series:

Adamson, Case No. 97.

1. 12/12/35, tubercle negative
2. 23/2/39, tubercle positive

Tubes not patent: radiograph pelvis negative: follow-up 6 years.

Barlow, Case No. 437.

1. 2/8/39, tubercle positive
2. 29/1/42, tubercle positive

Tubes not tested: radiograph chest negative: follow-up 2 years.

Bolton, Case No. 146.

1. 22/8/36, tubercle positive
2. 2/12/37, tubercle positive
3. 25/8/41, tubercle positive

Tubes not patent: radiograph chest negative: follow-up 5 years.

Burns, Case No. 96.

1. 18/11/35, tubercle positive

Tubes not patent: no radiographs: no follow-up.

Burrell, Case No. 106.

1. 20/2/36, tubercle positive

Tubes not patent: no radiographs: no follow-up.

Caul, Case No. 452.

1. 26/10/39, tubercle positive
2. 18/12/39, tubercle negative
3. 24/2/42, tubercle positive

Tubes patent: radiograph chest negative: follow-up 2 years.

Craig, Case No. 227.

1. 20/11/37, tubercle positive

Tubes not patent: radiograph pelvis negative: follow-up 4 years.

Forrest, Case No. 338.

1. 30/11/38, tubercle positive
2. 25/1/39, tubercle negative
3. 27/3/39, tubercle negative
4. 25/5/39, tubercle negative

Tubes not patent: radiograph pelvis negative: follow-up 3 years.

Haig, Case No. 347.

1. 18/4/40, tubercle positive
2. 24/2/42, tubercle positive

Tubes not tested: radiograph chest negative: follow-up 4 years.

Lyttle, Case No. 459.

1. 21/12/39, tubercle negative
2. 4/3/40, tubercle positive
3. 28/3/40, tubercle positive
4. 17/2/42, tubercle negative

Tubes not patent: radiograph chest negative: follow-up 2½ years.

Moss, Case No. 394.

1. 25/5/39, tubercle positive
2. 17/8/39, tubercle negative
3. 29/1/42, tubercle negative

Tubes patent: no radiographs: follow-up 2½ years.

McPherson, Case No. 393.

1. 11/5/39, tubercle positive
2. 19/5/39, tubercle positive
3. 3/11/41, tubercle positive

Tubes not patent: radiographs chest and abdomen negative: follow-up 2½ years.

Quinn, Case No. 21.

1. 10/9/35, tubercle positive
2. 28/6/38, tubercle positive

Tubes not patent: radiograph chest positive: follow-up 2½ years.

Sherlock, Case No. 454.

1. 23/9/41, tubercle positive
2. 8/12/41, tubercle positive

Tubes not patent: radiographs chest and abdomen negative: follow-up 2½ years.

Shields, Case No. 84.

1. 14/3/35, tubercle positive
2. 25/11/41, tubercle negative

Tubes not patent: radiographs chest and abdomen negative: follow-up 7 years.

E. Smith, Case No. 98.

1. 26/11/35, tubercle negative
2. 26/5/37, tubercle negative
3. 22/12/37, tubercle positive.
4. 26/10/39, tubercle negative

Tubes patent: radiographs chest and spine positive, abdomen negative: follow-up 6 years: died January 18th, 1942, "spinal abscess."

H. Smith, Case No. 469.

1. 15/4/40, tubercle positive
2. 31/7/41, tubercle negative
3. 7/8/41, tubercle negative
4. 27/8/41, tubercle negative

Tubes not patent: radiograph chest positive: follow-up 2 years.

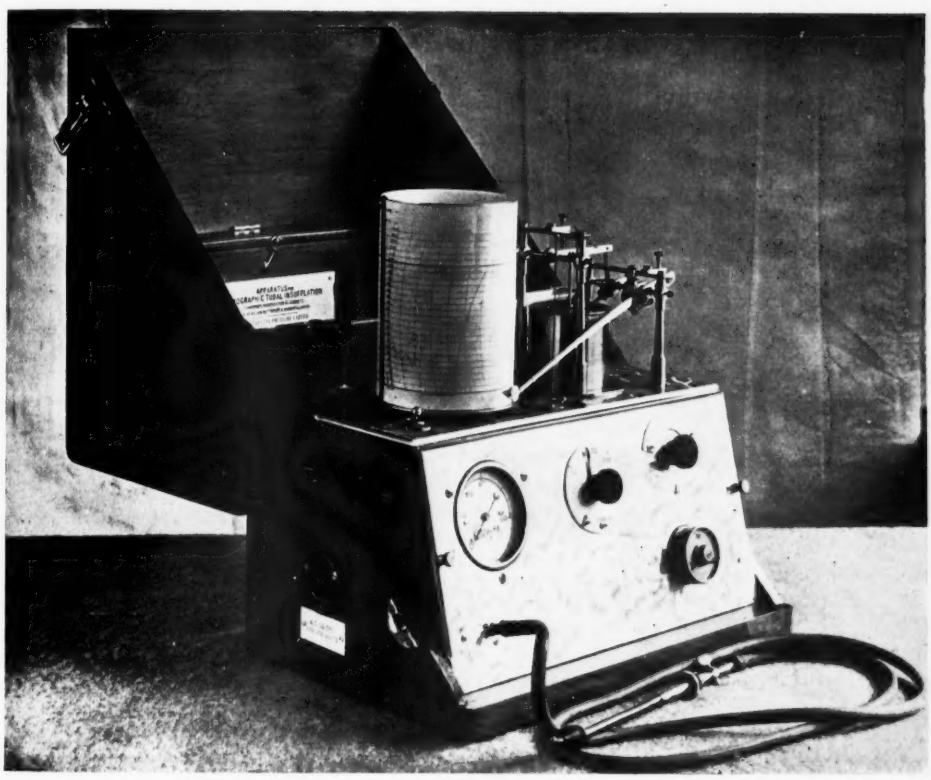


FIG. 1.

Kymographic apparatus for tubal insufflation. Carbon dioxide is supplied by a cylinder enclosed in a metal container on top of which is a registering manometer. The revolving drum is operated by an electric motor. The front panel of the instrument shows, reading from left to right, (1) dial indicating the pressure (and quantity) of gas in the supply cylinder, (2) a tap indicator to regulate accurately its rate of flow, and (3) knobs to turn gas on and off (the upper one controls supply within the regulating system).

FIG. 8.

"Lipiodols" from the same patient at intervals are illustrated in the above and in Figs. 8(*a*) and 8(*b*). The first photograph shows apparent left tubal blockage at the isthmus: the others, taken one and five months later, respectively, show bilateral

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FIG. 8 (*a*)

A.S.

FIG. 8 (*b*)

A.S.

FIG. 9.

Lipiodol showing tubal patency in new-born infants.
(Inset is actual size).

FIG. 8 (*b*)

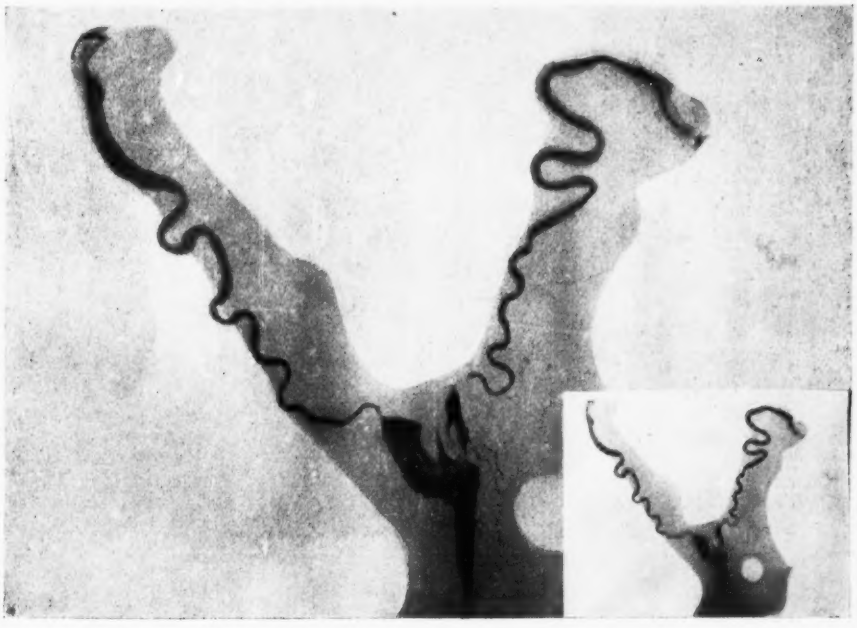
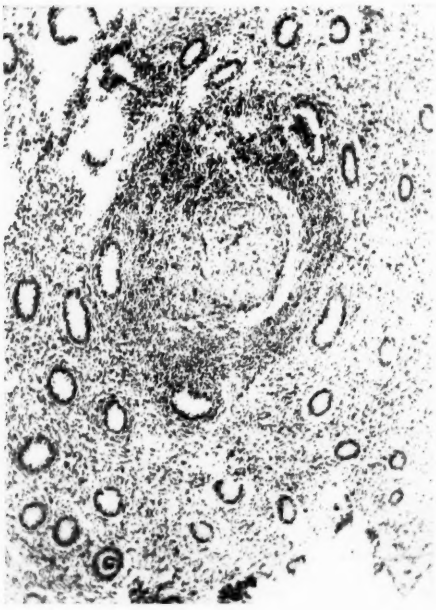


FIG. 9 (*a*)

A.S.

A.S.

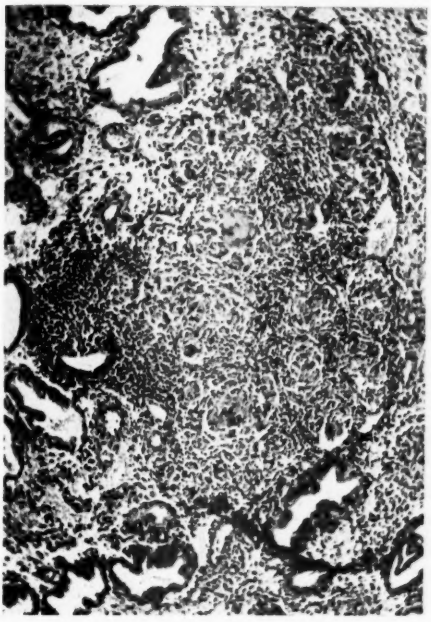
PLATE I—TUBERCULOUS ENDOMETRITIS.



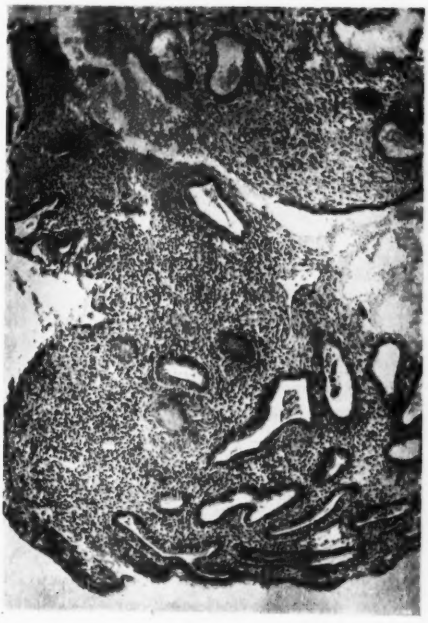
Burrell, Case 106.
Upper illustration: low power.
Lower illustration: high power of the tubercle follicle.

A.S.

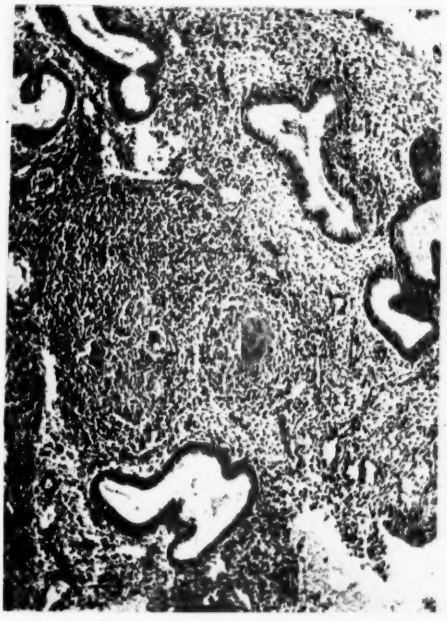
PLATE II—TUBERCULOUS ENDOMETRITIS.



Bolton, Case 146.



Caul, Case 452.



Moss, Case 394.

McPherson, Case 393.

A.S.

PLATE III—TUBERCULOUS ENDOMETRITIS.

Haig, Case 347.

Sherlock, Case 454.

Shields, Case 84.

H. Smith, Case 469.

A.S.

Thomson, Case No. 76.

1. 20/6/35, tubercle negative
2. 9/11/37, tubercle negative
3. 16/11/37, tubercle positive
4. 23/11/37, tubercle negative

Tubes not patent: no radiographs: follow-up 2½ years.

White, Case No. 323.

1. 10/11/38, tubercle positive
2. 5/12/38, tubercle positive
3. 21/6/39, tubercle positive

Tubes not patent: radiograph pelvis negative: follow-up 3 years.

Whitelaw, Case No. 353.

1. 22/10/41, tubercle positive
2. 28/10/41, tubercle positive

Tubes patent: no radiographs: follow-up 2 years.

The points which may be discussed in more detail now are:

(*a*) The high incidence of endometrial tuberculosis in sterility.

(*b*) The evidence that this estimated incidence is minimal.

(*c*) The duration of the disease.

(*d*) The effect of curettage.

(*e*) The results of search for tuberculous history, and for other tuberculous lesions.

(*f*) The relationship of endometrial tuberculosis to tubal occlusion.

(a) *The high incidence of endometrial tuberculosis in sterility.*

Sutherland has reported the finding of tuberculosis in one hundred endometria in a consecutive series of 7,670 (*including* sterility cases) giving an incidence of 1.3 per cent. It has already been pointed out that my series of 883 endometria shows an incidence of 5.3 per cent tuberculosis. Further analysis shows that endometrial tuberculosis is 15 times more common in sterile women than in those who are fertile.

(b) *The evidence that this incidence is minimal.*

In 17 of these patients biopsy was performed more than once: when performed twice it was tubercle positive on both occasions in 5 patients, and once positive and once negative in 2 cases: when performed either 3 or 4 times in the remaining patients, on 19 occasions it was tubercle positive and on 17 tubercle negative. Obviously therefore in many instances no evidence of the disease was found on single occasions. This occasional absence of evidence prompted further study of the endometria concerned. The paraffin blocks were re-imbedded and re-orientated so that further sections might be taken from the other end of the biopsy material. This was done in 12 blocks from 6 patients. Numerous sections were examined, but there was no evidence of tuberculosis in any of them, although many showed histological evidence of chronic endometritis. Further light in this connection was thrown by the examination of additional sections of the definitely positive biopsies: in several of the cases sections showed no evidence of tubercle follicles, although, in some, plasma and round cell infiltration was marked. Moreover, in several cases in which biopsy material was divided, negative histological findings and positive guinea-pig inoculation results were obtained. It may be concluded, therefore, that absence of signs of tubercular endometritis in any given biopsy is not evidence that the disease is not present and that the incidence figure of 5 per cent in my series is an absolutely minimal one. Moreover, in any case of primary sterility showing histological evidence of chronic endometritis, further sections should be examined for evidence of tuberculous lesions and, if such evidence is not found, additional biopsy should be performed. *Chronic endometritis in a case of primary sterility should be*

regarded as suspicious of tuberculous infection.

(c) *The duration of the disease.*

Endometrial tuberculosis was found to be still in evidence after the following lengthy periods of time in 6 patients: (1) $2\frac{1}{2}$ years, (2) 5 years, (3) $2\frac{1}{3}$ years, (4) 2 years, (5) $2\frac{1}{2}$ years, (6) $7\frac{1}{2}$ years. Follow-up also showed that not one sterility patient with endometrial tuberculosis became pregnant.

(d) *The effect of curettage.*

Although it was considered most improbable that even very thorough curettage of a tubercular endometrium would "cure" the condition, studies were carried out to observe the recurrence of the tubercle follicle and to determine its time-interval. Four sterile patients were investigated. The details are as follows:

CASE 1.

Mrs. C., aged 31 years, married 5 years, menstruation regular but scanty, sole complaint sterility, no history of tuberculosis.

August 21st, 1942. Curettage under anaesthesia, tuberculous endometritis, no tubal lesion detected, gas failed to pass on tubal insufflation.

September 1st, 1942. Menstruation.

September 24th, 1942. Endometrial biopsy showed tuberculosis.

CASE 2.

Mrs. F., aged 39 years, married 3 years, menstruation normal, sole complaint sterility, no history of tuberculosis, radiographs chest and abdomen negative.

September 14th, 1942. Endometrial biopsy showed tuberculosis.

September 22nd, 1942. Curettage under anaesthesia, endometrium removed from anterior wall showed tubercles, but tissue removed from posterior wall, right and left sides, did not. General curettage of the uterine cavity showed foci; gas passed, but at very high pressure on tubal insufflation.

October 4th, 1942. Menstruation.

October 12th, 1942. Curettage under anaesthesia, endometrium from anterior wall, posterior wall, right side and left side, each showed tubercular foci, insufflation repeated, showed as above.

CASE 3.

Mrs. H., aged 21 years, married 19 months, menstruation normal, sole complaint sterility, no history of tuberculosis but is losing weight, radiographs of chest and abdomen negative.

July 21st, 1942. Curettage under anaesthesia, tuberculous endometritis, bilateral tubo-ovarian swellings about size of hen's egg; gas failed to pass on tubal insufflation.

July 26th, 1942. Menstruation.

August 6th, 1942. Biopsy produced no endometrium.

September 3rd, 1942. Biopsy showed no evidence of tuberculosis.

September 24th, 1942. Biopsy (several attempts) produced no endometrium.

September 25th, 1942. Menstruation.

October 22nd, 1942. Biopsy showed tuberculous endometritis (numerous sections were examined, only one of which showed a focus).

CASE 4.

Mrs. L., aged 26 years, married 6 years, menstruation excessive, prolonged and irregular. Complaint: menorrhagia and sterility, no history of tuberculosis.

October 13th, 1942. Curettage under anaesthesia; tuberculous endometritis; no tubal lesion detected.

October 22nd, 1942. Curettage under anaesthesia, no evidence of tuberculosis in endometrium (many sections examined).

October 26th, 1942. Menstruation.

November 2nd, 1942. Biopsy showed no evidence of tuberculosis.

November 9th, 1942. Biopsy; tuberculous endometritis.

These findings may be summarized: tubercular endometritis was found to have recurred at the following intervals of time after thorough curettage under anaesthesia: (1) 34 days, (2) 20 days, (3) 3 months, and (4) 27 days. There seems little doubt therefore that reinfection of the endometrium

rapidly recurs after curettage. The question naturally arises as to the location of the focus from which reinfection occurs. Investigating this matter, careful enquiry was made into the previous history of the patient and a detailed search for tubercular lesions in other organs of the body was carried out.

(e) *The results of search for tuberculous history, and for other tuberculous lesions.*

In none of these cases was pelvic tuberculosis diagnosed or suspected when endometrial biopsy was performed. All were noted as enjoying good health and, with the exception of 3 cases, there was no history suggestive of tuberculosis in childhood or adolescence; the 3 exceptions were: (1) Case No. 452, aged 28 years, "pleurisy and gastro-enteritis" at age of 17 years; (2) Case No. 454, aged 29 years, "T.B. gland of neck" at age of 5 years; and (3) Case No. 76, aged 24 years, "tabes mesenterica" at age of 14 years (9 months in sanatorium). Radiographs of the chest in 10 cases showed no evidence of pulmonary tuberculosis in 7, but 2 showed apical tuberculosis of both lungs (Case No. 211 and Case No. 469) and the other calcified plaques at both apices (Case No. 98)—in the latter, radiograph of the spine showed Pott's disease: no calcified glands were seen in abdominal radiographs (4 cases) or in pelvic ones (4 cases).

(f) *The relationship of endometrial tuberculosis to tubal occlusion.*

I have left to the last the consideration of the incidence of tubal occlusion in cases of endometrial tuberculosis: in 18 of the 20 cases tubal insufflation was performed, and showed non-patency in 14 (78 per cent). In the second series of 27 cases, insufflation was performed in 22 and showed non-patency in 17 (77 per cent). Combining the two series, it will be seen that out of 40 cases insufflated, 31 showed tubal blockage, an incidence of 77 per cent. This extremely high incidence of occlusion suggested the possibility of an unsuspected sub-clinical tuberculous salpingitis as the source of reinfection of the endometrium, and this conception in turn led me to reconsider the possible aetiology of tubal occlusion from a new angle.

(IV) An Inquiry into the Causation of Tubal Occlusion.

There is, of course, no need to discuss tubal occlusion arising from gross tubal damage. The problem under consideration at the moment is the aetiology of blockage in tubes which appear normal on bimanual examination. In the past, it has been widely accepted that in most instances the occlusion of the lumen results from gonococcal salpingitis, or from tubal infection from a nearby-pelvic lesion (particularly appendicitis), or from congenital hypoplasia. The recent finding that endometrial tuberculosis is unexpectedly common (5 per cent) in sterile women suggested the possibility that tubal tuberculosis of a degree insufficient to be grossly recognizable, except on laparotomy, might be responsible for a much greater number of cases of tubal non-patency than is generally recognized, and led me to undertake certain investigations which I shall now discuss.

(1) *Gonococcal Salpingitis as a Cause of Occlusion.*

There is very little positive proof that, apart from gross tubal damage, gonococcal salpingitis is a common cause of tubal occlusion. It is unusual to obtain a history of any pelvic illness in a series of sterile women and, more important still, there is little direct evidence that the infection ever reaches the tubes in

more than a very small percentage of cases of gonorrhoea. There are few published data on this point, but with the co-operation of the Public Health Department of Glasgow I have been able to obtain the following figures which, I think, are of considerable significance. The records of acute gonorrhoea in women who attended the principal clinic from 1930 to 1937 were surveyed, with special reference to the incidence of pelvic involvement. There were only 5 cases of the latter in a total of 540 patients. A follow-up of the 5 cases revealed that 1 subsequently had 3 pregnancies, but that the others had not become pregnant. During the years 1938 to 1942 (inclusive) the total number of new cases of acute and chronic gonorrhoea in females over 15 years of age, attending the principal Glasgow municipal centre amounted to 987. Of these, there were 26 cases of acute pelvic involvement (2.6 per cent). In 775 consecutive cases of acute gonorrhoea, during the same period, there were 10 cases of salpingitis (1.3 per cent). Very careful observations have been made on this point since June 1941. Since that date a total of 979 cases have been treated, of which only 8 have developed an acute febrile pelvic lesion (less than 1 per cent).

Even if it is admitted that a number of mild pelvic infections may have occurred, the general conclusion appears to be that the gonococcus is seldom responsible for the occlusion of tubes which are not palpably thickened.

(2) *Congenital Hypoplasia as a Cause of Tubal Occlusion.*

The significance of this factor was first described and stressed by Clauberg (1938) who maintained that, in cases of infantile uterus, the tubes often share in the developmental deficiency and are consequently impermeable. There has been a vague general acceptance of Clauberg's theory, but I am not satisfied that it is correct. The following arguments may be raised against it:

(1) Clauberg's evidence was almost entirely radiological (apart from investigations on lower animals), (2) a large number of cases of uterine hypoplasia have shown normal tubal patency and function in kymographic insufflation, (3) radiographs frequently show patency in tubes presenting the long, thin, tortuous features of the "congenital hypoplastic" type, (4) in a small series of cases showing *definite* tubal blockage and treated by Clauberg's method with oestrogenic hormone none showed patency after treatment as claimed by him, and (5) tubal blockage associated with uterine hypoplasia need not be due to tubal hypoplasia but may be due to other causes e.g. sub-clinical tuberculosis, as will be discussed later. It is not disputed, of course, that follicular hormone produces proliferation of the mucous membrane and general hyperaemia of the Fallopian tubes, as Clauberg has shown, but the point at issue is whether the hypoplastic or infantile tube is essentially a non-patent structure or not. I have approached this question from three angles: (1) a histological study of the prepubertal tube, (2) insufflation of the tubes of the foetus and infant, and (3) kymographic insufflation in an unselected, consecutive series of unmarried women.

A. *The prepubertal tube.* Fallopian tubes were removed postmortem and sectioned from cases of the following ages: (*a*) a 7-months' foetus, (*b*) a foetus stillborn at term, (*c*) a child aged 2 days, (*d*) a child age 10 weeks, (*e*) 3 months, (*f*) $4\frac{1}{2}$ months, (*g*) 7 months, (*h*) 16 months, (*i*) 3 years, (*j*) 4 years, (*k*) 8 years and (*l*) 10 years. Sections were cut through fimbrial, ampullary and isthmial portions. The appearance of the tubes throughout the series are those of a patent structure and there is no evidence that canalization of the Müllerian ducts is often (if ever) incomplete.

B. *Insufflation of the tubes of the foetus and infant.* The material studied was obtained postmortem from a series of stillborn infants and neonatal deaths in the Glasgow Royal Maternity Hospital and from fatal cases in the Royal Hospital for Sick Children, Glasgow. The examination was carried out as soon as practicable after death, usually within a few hours. Twelve cases were insufflated. All showed tubal patency:

Age	Number
Five months' foetus	1
Stillborn	1
Four days	1
Six days	2
Seven days	1
Eight days	1
Ten days	1
Eleven days	1
Nineteen days	1
Two months	1
Four years	1

Skiagrams demonstrating tubal patency in two infants are shown (Fig. 9).

C. *Insufflation in unmarried women.* I wish to make it clear that no woman was admitted to hospital and subjected to this test simply for purposes of experiment. All the patients thus examined had been admitted for the treatment of some definite complaint, the commonest being dysmenorrhoea. The opportunity was taken at the time of operation to apply this test. One hundred and four have been studied to date, their ages ranging from 13 to 39 years. It was estimated that in over one third of the patients the uterus appeared to be of the small, hypoplastic type.

Insufflation showed that in all cases the tubes were permeable to gas. In 96 of them the gas passed at low pressure, but in 8 a certain degree of spasm appeared to be present, as evidenced by the fact that gas reached a high pressure before passing.

In conclusion it may be stated that the evidence obtained from these three separate lines of enquiry suggests that impermeability of the tubes is seldom a congenital defect.

(3) *Sub-clinical Tuberculous Salpingitis as a Cause of Tubal Occlusion.*

It will be remembered that, in the course of this investigation, unsuspected subclinical endometrial tuberculosis was found in a relatively high percentage (5 per cent) of sterile women. Now, since endometrial tuberculosis in general is almost invariably secondary to tuberculous infection of the tube, it is highly probable that sub-clinical tubal tuberculosis is present in at least 5 per cent of sterile women. Further, it is well known that endometrium often escapes infection even when the tubes are the seat of gross tuberculous lesions, and it is, therefore, highly probable that in sterile women the incidence of sub-clinical tubal tuberculosis is much higher than 5 per cent. This suggests the possibility that sub-clinical tuberculosis of the tube may be the cause of occlusion in a tube which appears normal to palpation. An endeavour was made to obtain positive evidence on this point, and two separate methods of investigation were utilized. First, the incidence of tubal occlusion in cases of endometrial tuberculosis was investigated and, second, histological proof of tuberculous infection was looked for in tubes which had been found to be blocked.

The incidence of tubal blockage in endometrial tuberculosis was found to be 31 in 40 cases, i.e. 77 per cent. This compares with an incidence of 38 per cent* over the total series of 500 sterile women, including those in whom endometrial tuberculosis was present.

The second line of evidence was more

* The corrected incidence has already been indicated as being barely 30 per cent and in a further unselected series 26.8 per cent.

difficult to apply, because only a small number of women were willing that an attempt should be made to restore patency of the tube by operation. So far I have had an opportunity of studying the histology of 4 such tubes, a small piece being removed in the course of salpingostomy. The series is too small from which to dogmatize, but nevertheless it is striking that all 4 specimens showed tuberculous infection.

In view of these findings I feel justified in putting forward the view that tubal blockage may, in a considerable number of cases, at any rate, be due to a sub-clinical tuberculous salpingitis.

(V) Seminal Analysis.

Examination of the husbands was performed by Mr. W. S. Mack at Glasgow Royal Infirmary in 114 cases of the total series of 500. The proportion is, unfortunately, small and, in view of the findings about to be described, unsatisfactory. But a study of the 114 cases, entirely unselected, ought to give information which may be regarded as representative of the larger series. The main reasons for the relatively small number of husbands examined were (*a*) in the earlier cases of the series the importance of this aspect of the subject was not sufficiently emphasized to the patient, (*b*) disinclination and often complete refusal of the male partner, on various grounds, and (*c*) since September 1939, war has made it extremely difficult to get more than an occasional case to attend.

Examination was particularly directed to general health, previous history, sexual life, genitalia and seminal fluid, but I do not propose to describe these findings in detail. However, fuller consideration will be given to those cases in which the results of seminal examination could be correlated to the findings in the partners and to the results of follow-up.

Seminal specimens were examined in 114 cases: 78 were normal (68.4 per cent), 15 were markedly deficient (13.2 per cent), and 21 showed complete absence of sperms-azoospermia (18.4 per cent). The arbitrary figure of 30 million sperms per c.c. was used as the basic distinguishing line between normality and marked deficiency, keeping close in mind, however, the fact that sperm morphology is as important if not more important than the mere count. However, it was found that in the "normal group" (over 30 million per c.c.) only in one case were the morphological characters abnormal.

The essential features of each of these groups are as follows:

A. Normal—78 Cases (68.4 per cent).

1. All showed a sperm count of over 30 million per c.c., most being between 100 and 160 million.

2. Sperm morphology was normal in all except Sim, Case No. 263, showing "an undue percentage of rounded heads; count 60 million."

3. Two cases showed numerous crystals (*a*) Oliver, Case No. 451 (on each of 3 tests), and (*b*) McDonnell, Case No. 419 (on one test, count being 70 million).

4. In 3 (Garth, Case No. 324; Hamilton, Case No. 331; and Stewart, Case No. 322), a large left varicocele was present. (The wives of the 2 latter had normal full-time pregnancies.)

5. Results of follow-up of wives:

Untraced, 6. *Pregnancy*, 17.

(All pregnancies went to normal full-time, except one that miscarried at 3 months and one that had to be terminated at 4 months for hyperemesis).

No pregnancy, 55.

(Twenty had non-patent tubes and of the remaining 35 with patent tubes 4 had anovular cycles and one had tubercular endometritis).

B. Markedly Deficient—15 Cases. (13.2 per cent).

1. All showed a sperm count of under 30 million, several of them being below 4 million.

2. Sperm morphology was normal in 6 but the others showed various abnormalities, e.g., aberrant, immature forms and head irregularities.

3. The test was done once in 5 patients, twice in six patients, thrice in 3 patients and on 4 occasions in one patient. Repetition of the test (within 6 months) invariably gave the same result.

4. One patient had a history of malaria, but none of the others presented features of note either in their medical history or on physical examination.

5. Results of follow-up of wives:

Untraced, 1. *Pregnant*, 3.

(One miscarried at one month, one miscarried at 2 months and one went on to full-time. In the last case, although the seminal specimen showed "many crystals, count of 28 million [repeated], many of which with rounded heads," pregnancy ensued within 2 months of the test).

No pregnancy, 11.

(Only one had non-patent tubes: all the others had patent tubes, but one of them had anovular cycles and one had tuberculous endometritis. One patient [Burt, Case No. 464] had curettage performed "on several occasions" in different hospitals for sterility—her husband had not been examined. The present investigation showed on 2 occasions a sperm count of under 20 million and poor morphology. Another patient [Moss, Case No. 394] had curettage performed 18 months previously: here also the husband's semen had not been examined.)

C. Azoospermia—21 Cases (18.4 per cent).

1. Seminal examination was performed once only in 9 patients, twice in 11 and 4 times in 1. In all cases sperms were entirely absent.

2. Four patients showed abundant crystals but no other deposits in the semen.

3. In 9 nothing abnormal was found either in the medical history or on physical examination. In 6, one or both testicles were small and soft; one had been operated upon for undescended testicles; 2 had a testicle removed on account of tuberculosis; 1 had an atrophic left testicle; 1 had bilateral gonococcal epididymitis 9 years previously and 1 had had uncomplicated gonococcal urethritis.

4. Results of follow-up of wives:

Untraced, nil. *Pregnant*, nil.

(Fifteen had patent tubes, 4 non-patent and in 2 tubal patency was not tested. One of the "patency-group" showed anovular cycles. Six had previously had a dilatation and curettage performed for sterility by other surgeons, without the male being referred for examination; indeed one of them had been curetted twice.)

(VI) The Results Obtained by a Follow-up Investigation.

Of the 500 cases, 409 were traced for periods from 3 to 9 years. Failure to trace the remaining 91 patients is very largely due to war circumstances, e.g. evacuation, absence from home on service or war work, being "bombed-out," etc. Loss of desire to become pregnant is a frequent cause of patients failing to report or even to reply to a follow-up letter.

Of the 409 cases traced, 116 became pregnant, i.e. 28.3 per cent. Their main features are summarized as follows:

1. Eighty-two were under 30 years of age and 34 were 30 years or older when first under observation.

2. The oldest was 40 years old (married 4 years)—she miscarried at 3 months.

3. Forty-nine were married 3 years or more; 17 were married 5 years or more; 1 was married 13 years (aged 35); (no patient married longer than this became pregnant).

4. Tubal insufflation was performed in 111; patency had been diagnosed in 82 and non-patency in 29—of the latter 23 had been insufflated under anaesthesia and 6 without it; hysterosalpingography was done in 4 of the 29, but showed tubal patency; the fallacy of a single finding of non-patency on insufflation is apparent from these figures, but the possibility of the therapeutic effect of insufflation must not be overlooked.

5. Pregnancy terminated in miscarriage in 18 of the 116, i.e. 15.5 per cent, but 4 subsequently had a full-time child; 1 further case had pregnancy terminated (in another hospital) for hyperemesis gravidarum and another for pre-eclamptic toxaemia at 7 months; thus 102, or 88 per cent, bore a child (2 cases had twins); one patient had 3 miscarriages and another 2—neither have since gone to term. Endometrium, removed premenstrually, in 15 of these cases showed normal features in all. Semen was examined in 4 husbands; it was markedly deficient in 2.

6. The sex incidence of the infants was approximately 46 per cent male and 54 per cent female.

7. *Time elapsing between insufflation and conception.*

15 pregnancies occurred within 1 month after insufflation; 11 within 2 months; 14 within 3 months; 2 within 4 months; 6 within 5 months; 7 within 6 months. A total of 55.

Thus, 40 of 111 pregnancies (36 per cent) occurred within 3 months of insufflation and 55 (50 per cent) within 6 months. During the following 6 months 24 became pregnant. It must not be overlooked, however, that in 36 per cent of the group of 111 cases more than 1 insufflation was performed; the data given above refer to the latest insufflation.

In view of the fact that repeated kymographic studies were made in many of the cases, it was almost inevitable that insufflation would be performed inadvertently in the first week or two of pregnancy. This happened in three patients, viz.:

1. *Haswell, Case No.* 92.

Twenty-second day of cycle, biopsy and insufflated (no kymograph); gas passed at 120 mm. Hg; normal full-time pregnancy.

2. *McLean, Case No.* 164.

Twenty-eighth day of cycle; biopsy and insufflated (no kymograph); gas passed at 80 mm. Hg; normal full-time pregnancy.

3. Jack, Case No. 326.

Eighteenth day of cycle, kymographic insufflation; gas passed at 90 mm. Hg with normal tubal contractions; normal full-time pregnancy.

8. In 5 patients who became pregnant neither insufflation nor lipiodol injection was performed: in 1, dilatation and curettage and perineoplasty was done and, in the others, only endometrial biopsy: the time elapsing between the procedure and conception was 28 months, 20 months, 1 month, 11 months and 12 months respectively.

Similarly, as with the kymographic tests, the nature of these studies—especially in the investigation of premenstrual endometrium—made it inevitable that biopsy would inadvertently be performed in the first week or two of pregnancy. This occurred in 6 cases: the endometria, of course, showed secretory changes; a definite decidual reaction in the stroma was noted in 1 only. One patient miscarried at 3 months but the other 5 had normal full-time pregnancies. (2, as already mentioned, had insufflation at the same time as biopsy). All but 1 had only 1 biopsy performed, the exception having 3 biopsies, viz. twenty-eighth day of cycle, thirty-fourth and forty-first; it was thought that the risk of miscarriage would be great in this case and so she was given 3 intramuscular injections of Progestin during a period of 6 weeks following the last biopsy; the remainder of her pregnancy was uneventful. One further case had biopsy attempted, when it was not known that she was at a very early stage of pregnancy, but no endometrium was obtained.

9. Of the 114 patients who had hysterosalpingography, 30 became pregnant. Lipiodol showed bilateral tubal patency in 25, unilateral fimbrial blockage in 3, unilateral isthmial blockage in 1, and 1 result was unsatisfactory. All had insufflation performed at least once prior to lipiodol injection and many of them also subsequently.

It is, therefore, impossible in these cases to apportion to these procedures possible therapeutic responsibility. However, in 14 of the 30 the interval between lipiodol injection and conception was sufficiently long (or subsequent insufflation was followed very quickly by pregnancy) to make it seem unlikely that hysterosalpingography was immediately or directly responsible for the sequel.

In concluding this account of the results of follow-up, consideration must be given to the 'unsuccessful' cases. Of the 409 patients traced, 293 did not become pregnant, i.e. 71.6 per cent. Factors completely preventing pregnancy were present as follows:

Tubal blockage	112
Azoospermia	17

(Four remaining "azoospermia cases" are included in the total of "tubal blockage," since both conditions were present.)

Thus of the 293 who did not become pregnant this event may be regarded as impossible in 129. In addition, the occurrence of anovular cycles, endometrial tuberculosis, and the finding of markedly deficient semen are obviously "major infertility factors"; these together account for 21 cases. Two husbands died within 2 years of their wives' first attendance at hospital.

Summing these cases gives a total of 152 in which pregnancy was either impossible or very unlikely. This leaves 141 cases in which, as far as investigation went, no reason was discovered for the infertility of marriage. Thus, although only 28.3 per cent of the 409 patients traced became pregnant, pregnancy occurred in 116 of 257 or 45.0 per cent of patients in whom no barrier to pregnancy was found. One further point, however, must be borne in mind, namely, that the incidence of azoospermia, anovular cycles and endometrial tuberculosis, already described, makes it reasonably certain that a further number of cases would have come into the group where pregnancy was impossible or improbable if more cases had been appropriately examined. Finally, in reviewing and analysing those cases in which pregnancy did not occur, the effect of war, mainly in respect of frequently separating partners in a hitherto sterile marriage but also in other directions, raises a totally incalculable factor.

Summary.

A study of a consecutive and unselected series of 500 cases of primary sterility has given the following main results:

1. Insufflation has revealed apparent non-patency in 38 per cent of cases.

2. Of 358 patients in whom biopsy was performed premenstrually 6.4 per cent exhibited anovular cycles.

3. Of 392 patients in whom biopsy was performed 5.1 per cent showed unsuspected tubercular endometritis.

4. Seminal examination in 114 husbands revealed normal characters in 68.4 per cent, marked deficiency in 13.2 per cent, and azoospermia in 18.4 per cent.

5. Of 409 cases traced 116, i.e. 28.3 per cent, became pregnant.

6. Pregnancy did not occur where anovular cycles or endometrial tuberculosis or azoospermia were present (with the exception of 2 cases of anovular cycles after treatment).

7. Of 293 sterile marriages, in 152, i.e. 52 per cent, infertility factors were found such as to render pregnancy impossible or very unlikely. If a greater number of cases had had endometrial biopsy and seminal examination performed there is little doubt that the infertility factors of anovular cycles, tubercular endometritis and azoospermia would have appreciably reduced

the figure of 141 cases in which, as far as investigation went, no reason was discovered for the infertility of the marriage.

More detailed study of the above series, combined with observations and experimental investigations of a further group of cases, have given the following principal results:

1. Repeated insufflations have shown that under similar conditions, e.g. the constancy of the rate of flow of the gas, there is a noteworthy constancy in the appearance of the tracings obtained. No great difference, either in the level at which patency is established, or in the appearance of tubal contraction waves is usually seen in any given patient when insufflation is repeated, even after several months (with or without anaesthesia). Increase in the rate of flow of gas may be followed by a marked increase in the patency-pressure level and by more active, deeper peristaltic waves, but is not invariable. Around ovulation-time (presumptive) more active or more frequent peristalsis may be seen. This also is not invariable, and there is no indication that there is any constant close correspondence between the type of tracing obtained and the stage of the endometrial cycle. On the other hand repeated insufflations have shed some light on the criteria of non-patency. The first point is that a single finding of non-patency, with or without anaesthesia, is not reliable. This has been proved by the subsequent occurrence of pregnancy or by the occurrence of a characteristic kymographic tracing of patency or by hysterosalpingography. Again, in cases of tubal patency, an isolated or occasional finding of apparent non-patency may occur. A fallacious finding of non-patency may be obtained at any point of the menstrual cycle, is not influenced by anaesthesia and is not due to excessive rate of flow of gas. In all reported series, except where two or more insufflations (and/or a hysterosalpingogram) established non-patency, dependency on a single finding of non-patency has given too high an incidence in the past. Our experience indicates that true non-patency exists in from 25 to 30 per cent of primary sterility cases (in a series of 1,063, assessed by insufflation).

2. The percentage of error in insufflation and in hysterosalpingography is about equal, but the error in the former is reliance on a single test, which error can be avoided by repeating the test, whereas the error in hysterosalpingography is in the reading of the plates and is not always remediable.

3. Since the completion of the original series, a further 491 consecutive and unselected cases of primary sterility have shown unsuspected endometrial tuberculosis in 27 (i.e. 5.5 per cent). This gives a total incidence of 5.3 per cent in 883 cases.

4. In cases in which gross tubal damage is not present, tubal occlusion is rarely due to gonococcal salpingitis or to congenital hypoplasia. Evidence is produced to show that blockage in a considerable number of cases is due to sub-clinical tuberculous salpingitis.

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The Pattern of the Contractions of the Pregnant Uterus under Spinal Anaesthesia and the Attendant Changes in the Reactivity of the Myometrium

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SPINAL anaesthesia has two readily demonstrable effects on the pregnant uterus, it releases contractions and it heightens the reactivity of the myometrium to various stimuli. In virtue of these effects spinal anaesthesia provides a method by which certain aspects of the physiology of the pregnant uterus can be studied, notably the pattern of the uterine contractions and the factors which maintain uterine quiescence during pregnancy. It is with these effects of spinal anaesthesia and their implications that the present paper is concerned, not with the clinical advantages or disadvantages of this form of anaesthesia.

The observations to be discussed have been made over a period of 6 years in a series of patients in whom pregnancy had to be terminated by abdominal section at various periods of gestation from the 10th week onward. In 18 of the cases pregnancy was of less than 28 weeks duration; these cases provided most of the material. Supplementary observations were made in about 20 cases of Caesarean section performed nearer term or during labour. For most of the cases spinal anaesthesia was used. Some of these operations, however, were performed under local or general anaesthesia, and the observations made in these cases served as controls of the special anaesthesia effects.

TECHNICAL DETAILS.

The solutions used for the spinal injections were either hyperbaric 10 per cent procaine in a dosage of 0.6 to 1 c.c., or hypobaric 1:1,500 percaine in a dosage of 7 to 10 c.c. The injections were given in the fourth lumbar interspace and the anaesthesia usually rose to 1 inch below the umbilicus. The abdomen was opened within 10 minutes of giving the injection. In doing this it was found necessary to exercise care not to press upon the abdominal wall or touch the uterus as the peritoneum was incised: otherwise by reason of the heightened reactivity of the uterus under spinal anaesthesia a contraction may start at the site of the trauma and spread locally, so masking or replacing the more spontaneous contractions which it is desired to watch.

On opening the peritoneal cavity a varying time up to 30 minutes was spent in watching the uterus for contractions. Sometimes in early pregnancy it proved troublesome to get the uterus into view without handling it, but by the use of the full Trendelenburg position and drawing the intestines out of the pelvis it could usually be induced to fall into view. No forceps were placed on the broad ligaments or the ovarian ligaments.

With a little experience the contractions were found to be readily recognizable. They appear as rather pale areas, often slightly raised above the general surface. Their presence and extent can be confirmed by a light touch, and while theoretically this is an undesirable thing to do, in practice it does not appear to disturb the pattern of the contraction, for the reason that once a contraction has begun, the contracting area becomes relatively refractory to slight mechanical stimulation.

In some cases, mainly those in which full exposure of the uterus was found difficult, or those in which the operation could not be prolonged for one reason or another, such as maternal distress, attention was not paid so much to the contractions elicited by the spinal anaesthetic as to the reactivity of the muscle to various forms of direct pressure, ranging from a light touch with a knife point to heavy pressure with a finger.

Before discussing the observations some consideration must first be given to the nature of the uterine innervation because of its bearing on the interpretation to be given to the spinal anaesthesia effects.

Spinal anaesthesia rising to the tenth dorsal segment paralyses every connection between the spinal cord and the uterus except for the slender path from the upper dorsal region of the spinal cord that may reach the uterus through the connection of the ganglionated sympathetic cord with the extrinsic nerves of the uterus. It seems likely that this connexion is not a motor pathway and as the present inquiry is concerned only with the motor innervation of the uterus, it may be left out of account for our purpose.

Recently this problem has been reviewed by Reynolds,[1] who concludes that the original observations of Langley and Anderson[2] are still valid, namely that the motor innervation of the uterus proceeds from a localized area of the cord, the third, fourth and fifth lumbar segments. The results of the present inquiry have been interpreted accordingly on the assumption that spinal anaesthesia paralyses all the motor pathways from the spinal cord to the uterus.

The second aspect of the uterine innervation which has a bearing on the interpretation to be given to the effects of spinal anaesthesia is the nature of this motor innervation. Is it single, consisting of only one type of nerve, or is it double, consisting of both excitatory and inhibitory fibres? This problem is still far from settled, though it would appear likely from the work of Cannon and Rosenbleuth,[3] Morison,[4] Kennard,[5] and Read and Ross[6] that it is single and that the varying types of response to nervous stimulation and denervation are due to the different adrenin-like substances liberated at the nerve endings, substances which are provisionally termed sympathin-E and sympathin-I, excitatory and inhibitory respectively. The particular substance liberated depends upon the particular physiological state of the uterus at the time of stimulation. In other words there is for any given physiological state of the uterus only one response to an alteration of its nervous control.

The constant effect of spinal anaesthesia on the human pregnant uterus is the release of contractions, and this would seem to point to two conclusions: one that the normal motor action of the central nervous system on the pregnant human uterus is inhibitory, the other that such an inhibition is a sustained action and not an intermittent one. It is of course important to stress the point that it is the human pregnant uterus that is under consideration, because it is well known that different animals react differently to nervous stimulation, and also that in many animals, though probably not in man, the phenomenon known as pregnancy reversal occurs, in which the

non-pregnant uterus responds differently to the pregnant uterus.

The whole problem of the effect of the nervous system on the pregnant uterus is still far from settled, and one thing that should be borne in mind in interpreting these spinal anaesthesia effects is that the uterus is not the only autonomic organ that shows a response. While the uterus is being watched for contractions under the spinal anaesthesia the small intestine too may be seen undergoing vigorous contractions. It is indeed likely that the uterus is not entirely a special case but that its behaviour will ultimately be interpreted by the same laws as apply to other plain muscle effectors, subject of course to the special conditions imposed by pregnancy.

The description that follows is necessarily a composite one. Circumstances may arise, for example the anaesthesia may start to fade, which may make it necessary to stop the observations and finish the operation. Again, with increasing experience of what to look for, the operations done later in the series yielded more information than the earlier ones. For these reasons the details of individual operations are omitted.

The observations may be described and discussed under the following headings, the order being arbitrary, all the observations and their interpretations being closely allied.

1. The pattern of the contractions.

2. The frequency of the contractions at various stages of pregnancy.

3. The changes in the myometrial reactivity to mechanical stimulation.

4. Nervous inhibition and spontaneous abortion.

1. *The Pattern of the Contractions.*

Once a spinal anaesthetic has taken effect, usually within 5 or 10 minutes from first giving the injection, orderly contractions may commence. These contractions are not however of the same type throughout pregnancy. Up to the twentieth week they appear as travelling waves following a defined path. Later in pregnancy this wave pattern disappears, and the contractions now appear as mass contractions of the whole corporeal muscle. The explanation of this change in pattern will need consideration later.

The contractions which are seen in early pregnancy appear to start in two symmetrical areas, each situated on the lateral wall of the uterus in the neighbourhood of the uterine end of the Fallopian tube. From each of these areas one contraction spreads inwards and slightly downwards over the anterior wall of the uterus till it reaches the mid-line. It there fuses with its fellow from the opposite side, so that there is produced a V-shaped or sometimes a transverse contracting ridge across the front of the uterus at the intertubal level. At the same time similar contractions spread from the tubal areas across the back of the uterus and meet in the mid-line to form another V-shaped or transverse ridge on the back of the uterus. At this stage the fundus can be seen still relaxed and soft between the anterior and posterior transverse ridges. It may remain in this condition; sometimes however a median contraction may spread from the anterior transverse contraction, pass upwards over the summit of the uterus and fuse with a similar contraction rising from behind to form a median ridge over the fundus. If this takes place the upper half of the uterus becomes slightly heart-shaped.

From each transverse ridge a median contraction, three-quarters to one inch in width, then extends downward, one on the anterior, one on the posterior surface of the uterus, and after a period of roughly 4 minutes from the start of the contraction these mid-line contractions reach the level of the internal os. When they are fully

developed the uterus may indeed appear quite heart-shaped due to the contractions shortening the uterus in the mid-line; sometimes almost a bicornuate appearance is simulated. The anterior median contraction is the more constant; the posterior does not always develop.

From the median ridges usually one, but sometimes two, secondary circular waves may appear and spread laterally around the uterus, one about its middle, the other above the level of the internal os.

While the lower ends of the median contractions are still developing the upper ends may fade and the original nodes near the insertions of the Fallopian tubes reappear as separate contracting areas. The duration of the contraction varies in the different parts of its course. The secondary transverse contractions fade first, then the median contractions, and last of all the primary upper transverse contractions. In an excitable uterus the nodes near the Fallopian tubes from which the waves start may remain contracted until the next spontaneous wave begins; they may indeed remain contracted throughout the period of observation. The time taken for a contraction to appear, develop and fade varies, but 5 minutes is an average duration. After a varying interval, usually of about 10 minutes at the tenth week of pregnancy, a second contraction begins and follows the same course.

After the middle of pregnancy has been reached the contractions tend to depart from the pattern observed in the early weeks and to conform to the type of contraction seen in labour, a mass contraction in which all parts of the myometrium appear to contract simultaneously.

In those cases in which the abdomen was opened under local anaesthesia no contractions were observed. This is not to say that spontaneous contractions do not occur, indeed it is well established that they do, but they are quite infrequent and the chances of synchronizing a laparotomy with a spontaneous contraction occurring in a uterus with normal innervation must be correspondingly slight.

There is one question that calls for consideration here. How far are these contractions comparable to the truly spontaneous contractions of normal pregnancy? No certain answer can be given to this question but there are two sets of observations which make it likely that they are strictly comparable. In the first place the contractions under spinal anaesthesia are orderly and rhythmical, in the second a number of cases of normal labour have been observed following cord transection, i.e., under conditions comparable to those produced by spinal anaesthesia.

What, then, is the morphological basis of the wave contractions seen in early pregnancy, and what determines the change from a wave pattern to the mass contraction of later pregnancy?

The pattern of the contractions seen in early pregnancy appears to correspond closely to the contractions of the rhesus monkey in labour as described by Ivy, Hartman and Koff.[7] These authors describe a wave of contraction formed by the fusion of two waves starting bilaterally and synchronously from areas located in the region of the Fallopian tubes. These areas, termed by the authors "pace-makers," are situated about 1.5 cm. ventral and cranial to the insertion of the tubes. As each wave approaches the mid-line the corpus shortens longitudinally, and a circular peristaltoid wave appears at the level of the round ligaments and travels downwards. This longitudinal shortening may correspond to the median longitudinal ridge described in the present communication. Ivy describes the circular wave as "peristaltoid" rather than peristaltic, because it has been established that there is no conducting

bundle or other morphological structure in the uterus which would subserve a true peristaltic wave, i.e., a wave of contraction preceded by a wave of relaxation.

Hofbauer's[8] claims to have found a conduction bundle in the uterus have never been substantiated histologically (Reynolds[9]), and to some extent the name "pace-maker" sometimes given to the primary nodes of contraction in the uterus is only a syllogism borrowed from our knowledge of the conducting system of the heart. Reynolds, Sanford and Kaminester[10] too have shown that the motor fibres innervate the myometrium only locally, and do not contribute to any widespread intramural plexus. The question then follows: how is it that if there is no conducting bundle with properties different from the surrounding muscle, the waves travel along a set path? If the uterus is examined under spinal anaesthesia immediately after the foetus and placenta have been removed it is often possible to see the anatomical structure of the uterus which provides the path. The uterus contracts down vigorously, but the contraction is still not uniform, and the median transverse contractions stand out so sharply that the front of the uterus may present a symmetrical series of depressions on either side of the mid-line, separated by thick ridges of contracting muscle. In other words the pattern of the travelling waves is due to their spread along the parts of the uterus where the muscle fibres are most condensed. In the depressed areas the uterine wall is thinner. The release of the intrauterine pressure, allowing the thinner areas to fall in, now discloses the anatomical pattern.

As Ivy points out, the contraction pattern can be correlated with the development of the uterus from the two Müllerian ducts and the spiral interlacing of the fasciculi, whereby the muscle fibres become more closely packed in certain areas.

There is some experimental evidence supporting the view that there are gradients of activity in the pregnant uterus. Morison,[4] using preparations of the rabbit's uterus showing large spontaneous contractions of low frequency, found that in most preparations one end, usually the ovarian, contracted first. The ovarian end has a faster rhythm, and according to Morison must be regarded as the usual "pacemaker" of the oestrous uterus. On the other hand, Robson[11] in his work on the behaviour of isolated strips of the human pregnant uterus found no differences at parturition between strips from the upper and lower segments. He found that often different strips from the same region of the uterus reacted differently to the same dose of oxytocin.

The next question that arises is why the contractions start where they do at the primary nodes, rather than at other points along the paths which the travelling contractions take. Here again the same objection arises as when the paths of the contractions were under consideration, namely, how can we invoke the activity of a "pacemaker" in the absence of any specialized structure in the paratubal areas?

The explanation may be that nervous inhibition is not exerted uniformly on the whole uterus but mainly on the nodal areas, the "pace-makers." Removal of this inhibition by spinal anaesthesia allows these areas to begin contraction at their natural rate, and the contractions so initiated are then propagated along the pattern laid down by the spinal interlacing of the Müllerian ducts.

The change in the pattern of the contractions from the travelling wave of early pregnancy to the mass contraction of late pregnancy has been described. After the twentieth week the uterus, even when suddenly emptied, no longer responds with a

patterned contraction, but with a uniform contraction of the whole corporeal musculature. It now behaves as a syncytium (Morison[4]), and it is clear that in the second half of pregnancy all the muscle fibres have become equally reactive. The change is due to the changed anatomical or mechanical conditions obtaining in later pregnancy. This alteration is fundamentally due to the fact that, despite the enormous increase in the size of the uterus that occurs as pregnancy proceeds, there is no corresponding increase in the total number of muscle fibres in the uterus. There is in fact some evidence that there is no new formation at all of muscle fibres except perhaps at the very start of pregnancy. Every muscle fibre of the uterus accordingly becomes of importance, takes place in the general hypertrophy and becomes equally reactive. When this has taken place and all parts of the uterus have become equally reactive, nervous inhibition loses its importance in imposing a pattern. Mechanical factors such as the intrauterine tension now assume an importance they do not possess earlier. In other words the mass contractions of later pregnancy are evidence of a myometrium of a uniform reactivity.

Newton[12] inclines to the view that it is mechanical factors which are responsible for the lowering of uterine reactivity as pregnancy proceeds. Examining the pregnant guinea-pig uterus, he found that, while the non-pregnant horn showed fairly regular and maximal contractions, in the pregnant horn constant spontaneous contractions were seen in early pregnancy alone; later they became less frequent and often ceased altogether.

There is a series of experiments by Painter and Harne[13] relating to the significance of mechanical factors. Using the pregnant rat these workers were able to relate the frequency of spontaneous contractions to the degree of intrauterine tension. With a high intrauterine tension they noted repeated contractions. When the circular muscles contracted the intrauterine tension rose and, as long as this tension remained high, rhythmic contractions of the longitudinal muscles continued.

In contrast to this change in the reactivity of the uterus due to mechanical factors the present inquiry produced some evidence that the degree of nervous inhibition diminishes as pregnancy proceeds. The change in the pattern of the contractions would accordingly appear to be due to two related causes, the alteration in the anatomy of the uterus whereby a state of uniform reactivity replaces the state where the heightened reactivity is greatest along the lines of the muscle condensations, the second the decrease in the relative efficacy of nervous inhibition, a decrease discussed in the next section.

2. *The Frequency of the Contractions at Various Stages of Pregnancy.*

The dynamic effect of spinal anaesthesia is not constant throughout pregnancy. It is most marked in the very early weeks, and up to the twelfth week regular contractions are constantly observed. After the sixteenth week the contractions only occur erratically and they may not indeed be elicited again until quite late in pregnancy, usually about the thirty-sixth week, when the spinal anaesthesia effect reappears and spontaneous contractions of the mass pattern are released.

In contrast to these changes in reactivity under spinal anaesthesia as pregnancy progresses Robson[14] found that no stage of pregnancy is characterized by any definite degree of spontaneous rhythmic activity of isolated muscle strips. The explanation of the difference must be that the mechanical conditions of isolated muscle strips differ from those of the intact uterus. Robson stresses that changes in the reactivity of

the uterus may not involve the reactivity of one particular system but the reactivity of a definite muscular or neuro-muscular system.

This change in the spontaneous reactivity of the uterus under spinal anaesthesia supports the view already expressed that nervous inhibition is of less importance in the maintenance of uterine quiescence in late than in early pregnancy. In early pregnancy it is the main factor in keeping the uterus from contracting. Later the natural contractility of the myometrium becomes less, and suspension of nervous inhibition no longer releases regular contractions until the end of pregnancy.

Such a view conflicts to some extent with the generally accepted opinion that it is progesterone that is responsible for the early quiescence of the uterus. While there is much experimental support for the conclusions of Knaus about the functions of the corpus luteum there is still some room for criticism of the view that progesterone is solely responsible for uterine inhibition. Robson, for instance, in his studies on the reactivity of the uterus, concludes that luteal hormones may not be responsible after the very early weeks. Moreover in clinical practice progesterone, though perhaps the best substance as yet available for keeping the uterus at rest, often is of little avail either in stopping bleeding or inhibiting contractions.

3. *The Changes in the Myometrial Reactivity to Mechanical Stimulation.*

The general effect of spinal anaesthesia is to heighten the reactivity of the myometrium to trauma. The slightest pressure such as a light scratch may sometimes set up a linear contraction. Deeper pressure or squeezing the uterus is still more effective, while under local or general anaesthesia an equivalent trauma has no such equivalent effect. This would seem to show that nervous inhibition not only prevents the uterus from contracting spontaneously and expelling its contents, but also protects the uterus from the effects of casual mechanical traumata, traumata which in the absence of such nervous inhibitions would set up locally spreading contractions which in turn might start an abortion.

There are two further points about the heightening of the reactivity of the uterus to mechanical stimulation. The first is that the effect is greatest in early pregnancy and wanes as pregnancy proceeds, a change corresponding to the progressive decrease in the frequency of the spontaneous contractions. The second is that the effect is more marked along the track of the travelling contractions of early pregnancy. The heightening of reactivity is most pronounced in the tubal areas and the midline both on the anterior and posterior walls of the uterus.

4. *Nervous Inhibition and Spontaneous Abortion.*

In the present series there were 2 cases in which the contractions released by spinal anaesthesia appeared to cause a partial separation of the placenta, manifested by haemorrhage into the choriodecidual space.

The first patient, a woman with phthisis, was 13 weeks pregnant. Spinal anaesthesia was given in the usual way. On opening the abdomen strong uterine contractions were observed. About 20 minutes later the uterus was quickly opened by a single incision down to the chorion. A recent blood clot was present between the placenta and the uterine wall. Prior to the operation the patient had had neither pains or bleeding.

The second patient, suffering from mitral stenosis, was 14 weeks pregnant. A similar

choriodecidual haematoma was observed under similar operative conditions.

It is of course a truism that the cause of some cases of threatened abortion is a failure of one or other of the factors which maintain uterine quiescence. As in the case of the cause of the onset of labour the essential problem is not why the uterus expels its contents, that being a function of all plain muscle effectors, but how is it prevented from doing so before. The view that progesterone is mainly responsible for the quiescence of early pregnancy and the frequent disappointments attending progesterone therapy have been referred to. The main thesis of the present study is that it is nervous inhibition of the uterus which is primarily concerned with keeping the uterus at rest.

There is no doubt that many abortions and indeed many abortion sequences are spontaneous in the sense that their cause cannot be discerned, no maternal ectrotic factor can be found and the embryos appear normal. Often the abortions in this category follow some slight general shock or trauma. It may well be that some of these cases of spontaneous abortion are due to the sudden release of uterine contractions arising from the suspension of nervous inhibition. There is clearly a positive correlation between the period of pregnancy at which spontaneous abortion occurs and the phase of pregnancy at which paralysis of nervous inhibition by spinal anaesthesia is most effective in releasing contractions. Later in pregnancy, when the reactivity of the uterus is lower and mechanical and other factors become responsible for keeping the uterus quiet, the chances of spontaneous abortion become much less. Again the only effective way of treating a truly spontaneous abortion sequence is to keep the patient in bed and protect her from all accidental trauma. If this view is correct it may be that further developments in the treatment of these cases will come from an increase in the knowledge and use of the sympathominetic drugs in supplementing or replacing nervous inhibition.

Summary.

1. The effects of spinal anaesthesia suggest that the action of the central nervous system on the human pregnant uterus is one of sustained inhibition. This inhibitory effect is most pronounced in early pregnancy, up to about the sixteenth week, reappearing nearer term. It is an important factor in the maintenance of uterine quiescence, and it is suggested that some cases of spontaneous abortion are due to a sudden suspension of this nervous inhibition.

2. The contractions released by spinal anaesthesia are of two types. In early pregnancy the contractions appear as travelling waves in a pattern which can be correlated with the Müllerian architecture of the uterus, the contractions appearing to spread along paths where the muscle fibres are most condensed. These wave contractions start in symmetrical areas near the Fallopian tubes. As an answer to the dilemma of why the contractions should begin where they do in the absence of any specialized structure which could be called a "pace-maker," it is suggested that the nervous inhibition is primarily exerted on these areas.

The contractions of late pregnancy are mass contractions affecting all parts of the upper segment equally without dominance of one area over another. The change in the type of contraction is mainly due to an alteration of the mechanical conditions of the muscle fibres, in part to a diminution in the relative importance of nervous inhibition.

3. The reactivity of the myometrium to mechanical stimulation is heightened by

spinal anaesthesia. This increased reactivity is most marked in early pregnancy and along the path of the travelling waves. It is suggested that nervous inhibition of the uterus is one of the ways in which an early pregnancy is protected from casual traumata, traumata which otherwise would set up spreading contractions which in turn might determine an abortion.

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The Occurrence and Significance of Clostridium Welchii in the Female Genital Tract

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THIS investigation was undertaken in order to determine the frequency of occurrence of Cl. welchii in the upper vagina of puerperal women; the relation of the presence of the organism to the occurrence of symptoms during the puerperium; and, as a control series, the frequency of occurrence of the organism in the upper vagina of pregnant and non-pregnant women.

Eight hundred and forty-three swabs were examined by films, and by aerobic and anaerobic cultures. Though some cervical swabs were included in our material, most specimens were high vaginal swabs, obtained by vigorously swabbing the fornices. They were taken in the maternity wards as a routine measure when the patients showed a rise of temperature, with the primary object of finding or excluding group A haemolytic streptococci. The opportunity was taken of making anaerobic cultures also, specially for the growth of Cl. welchii.

In order to determine whether the delivery was responsible for an increase in the incidence of Cl. welchii it would have been necessary to take high vaginal swabs just before and after delivery, but this was not practicable. In order therefore to compare the incidence of the organism in the puerperal vagina with that in the pregnant or non-pregnant vagina a series of 600 high vaginal swabs from pregnant women under treatment for leucorrhoea, and from patients in the clinic for venereal diseases, was examined in the same way, making a total of 1,443 swabs.

It is well known that Cl. welchii—just as Cl. tetani—can and does live in the human intestinal canal as a harmless commensal. Little work has been done on the occurrence of Cl. welchii elsewhere in or on the human body, but different research workers have traced the bacillus in material obtained from the skin and mouth, and in bile and urine (Wrigley,[1] and in the urine of a case examined by the writer).

The modern textbooks are not very informative as to the occurrence of the organism in the birth passages. Blair Bell[2] considers the vagina to be sterile. Topley and Wilson[3] do not even mention Cl. welchii in puerperal infections, while Curtis[4] states that the organism is rarely present in the normal vagina. And yet Cl. welchii has been frequently obtained in cases of abortion and puerperal infection, and has also been found repeatedly in normal labour cases (Schottmüller,[5] Lehmann and Fränkel,[6] Lehmann,[7] Falls,[8] Wrigley,[1] Peckham,[9] Bysshe,[10] and Sadusk and Manahan[11]).

In Table I the results of different investigators are set forth. It is apparent from these figures that the given percentages vary considerably. The incidence of Cl. welchii in uncomplicated deliveries varies from less than 1 per cent in Peckham's series to nearly 9 per cent in that of Sadusk and Manahan. The average in the four

TABLE I.*

	Number of swabs	Clostridium welchii positive	Percentage
Uncomplicated deliveries:			
Peckham (1936) ...	545	3	0.62
Falls (1933) ...	270	15	5.6
Bysshe (1938) ...	547	25	4.5
Sadusk and Manahan (1941)	219	19	8.7
Total	1581	62	3.92
Puerperal infections:			
Wrigley (1929) ...	69	13	19.0
Peckham (1931) ...	775	5	0.65
Total	844	18	2.04
Abortions:			
Schottmüller (1910)	145	7	5.0
Lehmann and Fränkel (1924) ...	1664	323	19.5
Lehmann (1926) ...	580	106	18.0
Falls (1933) ...	—	—	33.0

* Only papers from 1910 onwards have been included.

series is about 4 per cent. The incidence in puerperal infections varies even more, from less than 1 per cent in Peckham's series of 775 cases to 19 per cent in Wrigley's much smaller series. There is a high incidence in cases of abortion.

Methods.

For culturing anaerobic organisms the high vaginal swabs were swirled round several times in ordinary broth, which was then transferred by pipette into Robertson's cooked meat medium and into tubes of "deep" milk. Direct smears were made and stained by Gram and other methods, and blood-agar and MacConkey plates, and agar and laked blood agar slopes inoculated. In only 3 out of the 50 positive cases were the bacilli found in the direct film.

The anaerobic cultures were examined after 24 and 48 hours' incubation. It was found that for ordinary purposes incubation for 24 hours is quite sufficient to obtain a good growth of Cl. welchii, if they are present at all. It should be noted however —though in rare cases the reverse holds good—that the meat broth is much superior to the milk culture, the latter frequently failing to show gas bacilli on first culture and only developing a stormy clot after subculturing from the meat broth. The iron-broth medium[12] which affords an easy method for "aerobic" cultivation of anaerobes is also inferior to the meat broth. As a medium for subsequent subculture, however, it was found to be very satisfactory. Contrary to the experience of other workers the thioglycollate medium[13] did not prove a good method for the "aerobic" cultivation of Cl. welchii, either as a primary culture or for subculture.

Reddening of the meat in Robertson's medium appeared to be an inconstant factor, difficult to judge except when present in marked degree. Constant, however, was the formation of gas, and in the deep milk the smell of butyric acid, as well as the haemolysis in fluid and on solid media.

The first 4 strains were tested for their pathogenicity. 0.1 c.c. of the broth culture was injected intraperitoneally into white mice. Three mice died within 24 hours, the fourth after 3 days. From the first 3 animals a pure growth of Cl. welchii was obtained in cultures of the heart blood and spleen. The fourth showed a mixed infection with anaerobic streptococci.

The biochemical properties of 7 strains were as follows: glucose, lactose, maltose, saccharose and dextrin were always fermented, starch, glycogen and glycerin in 6 cases, while no reaction occurred with mannite. A curious and constant phenomenon was the fermentation of inulin in peptone water, but not in Hiss's serum medium.

Results.

As stated, these 843 high vaginal swabs were taken during the puerperium from

patients showing a rise of temperature above normal. There are included therefore patients of all categories of morbidity, from practically normal cases to cases of severe sepsis and septicaemia.

Cl. welchii was isolated on 50 occasions, that is to say in nearly 6 per cent. Table II gives the distribution over 22 months.

TABLE II.

	Number of swabs	Clostridium welchii positive	Percentage
August, 1941	13	2	15.0
September	40	1	2.5
October	37	3	8.0
November	43	2	4.5
December	62	4	6.5
January, 1942	37	3	8.0
February	23	3	13.0
March	23	1	4.0
April	43	3	7.0
May	24	3	12.5
June	34	2	6.0
July	47	1	2.0
August	46	1	2.0
September	33	1	3.0
October	35	1	3.0
November	41	1	2.5
December	54	4	7.5
January, 1943	43	3	7.0
February	34	1	3.0
March	44	4	9.0
April	40	3	7.5
May	47	3	6.0
Total	843	50	5.93

It will be noted that the percentage varies from 2.5 per cent to 15 per cent—the numbers are, of course, small—and that the occurrence of Cl. welchii was highly irregular and appeared to have no connexion with the seasons of the year. In Table III are shown the results of examination of 300 high vaginal swabs from women attending the Venereal Diseases Clinic, and 300 from pregnant women under treatment for leucorrhoea. None of these women could be regarded as normal, and manual examination and therapeutic vaginal instrumentation were constantly being carried out in all of them. But in none was there any clinical evidence of Cl. welchii infection. The table shows, however, in both series a higher incidence of Cl. welchii than in the puerperal cases: over 7.5 per cent in the venereal cases, and over 6 per cent in the pregnant women. It must be pointed out that—as the figures in brackets in Table III indicate—all obtained percentages lie within the standard deviation. Thus one would hesitate to make too definite a statement as to the accidental contamination of the vagina with Cl. welchii.

TABLE III.

Wards	No. of swabs	Cl. welchii positive	Percentage*
Venereal diseases clinic	300	23	7.67 (±3.43)
Antenatal clinic	300	19	6.33 (±3.43)
Maternity department	843	50	5.93 (±3.43)

* The figures in brackets give the standard deviation.

In Table IV are set out details of the cases from which Cl. welchii was obtained. As regards length of labour, this shows no important connexion with the finding of Cl. welchii. In only 18 per cent of the cases did labour last longer than 36 hours, and in only an additional 8 per cent, longer than 48 hours.

Less than one-fifth (18 per cent) of all Cl. welchii positive cases were uncomplicated deliveries. It seems fair to suggest that, if high vaginal swabs had been taken in more cases of this kind, a greater number of gas bacilli would have been isolated. But, neglecting for a moment this probability, the obvious fact is that, as Table IV shows, 40 per cent of all Cl. welchii cases belonged to the category of manual and instrumental interference.

As regards temperature, only about a quarter of the positive patients (26 per cent) showed a rise above 100°F. In none

TABLE IV.

	Spontaneous delivery	Manual and/or instrumental interference	Caesarean section	Retained placenta or membraneous tissues	Postpartum haemorrhage	Prematurely ruptured membranes	Macerated foetus	Total	Total in percentage
Number of positive swabs	9	20	9	4	3	1	1	47	94
Percentage of positive swabs ...	18	40	18	8	6	2	2	–	94
Labour longer than 36 hours ...	3	7	1	1	1	–	–	13	26
Labour longer than 48 hours... ...	2	5	1	–	1	–	–	9	18
Temperature above 100°F.	2	5	4	1	1	–	–	13	26
Other organisms:									
B. coli	3	17	4	2	3	1	1	31	62
B. proteus	–	–	1	–	–	–	–	1	2
B. pyocyaneus	–	–	1	–	–	–	–	1	2
Enterococci	1	2	–	1	–	–	–	4	8
Anaerobic streptococci	3	7	5	1	1	–	–	17	34
Haemolytic streptococci ...	1	–	2	1	–	1*	–	5	10
Incidence of Clostridium welchii:									
First week	8	17	7	4	3	1	1	41	82
Second Week	1	1	2	–	–	–	–	4	8
Third week	–	2	–	–	–	–	–	2	4
Second swab positive:									either
First week	1	3	2	1	1	–	–	8	40 or 32
Second week	–	1	1	–	–	–	–	2	8
Third swab positive	–	1	1	–	–	–	–	2	–
Fourth swab positive	–	1	–	–	–	–	–	1	–
Second swab negative	1	10	2	1	1	1	–	16	60
Positive cases, particulars unknown	–	–	–	–	–	–	–	3	6

*The streptococci of this case only belonged to Group A

was there clinical evidence of Cl. welchii infection. None of the patients died or was seriously ill. All made a good recovery, the speed of which was in keeping with their general health and the complications of their labour.

It will be noted that Cl. welchii was isolated mostly during the first week after delivery. But most of the swabs were taken during that period, so that too great stress should not be laid on this, though the first week postpartum is the time in which one would expect the act of childbirth to cause such contamination. Of greater significance is the fact that in nearly two-thirds of the cases examined (16 out of 26) the organisms could no longer be isolated from a second swab, and in two cases a third swab was also negative.

The nature of the organisms present in the Cl. welchii positive cases is of interest and importance: Bact. coli was also present in 62 per cent, anaerobic streptococci in 34 per cent and haemolytic streptococci in 10 per cent. Other workers have also observed an association between Cl. welchii and Bact. coli, and it appears likely that the origin of both organisms is from the bowel of the patient herself. It might be thought that, in that case, enterococci should be present more frequently than in the 8 per cent of cases obtained, but it is likely that in the puerperal uterus and its environment, conditions are more to the liking of Cl. welchii and Bact. coli and anaerobic streptococci than of the enterococci. It is noteworthy that though haemolytic streptococci were present in 10 per cent of the positive cases, group A haemolytic streptoccocci were present in only 1 case. It is our experience, as it is of others, that in genuine group A streptococcal puerperal sepsis the streptococci are present in the uterus in very large numbers and other organisms are scanty or absent.

One other point as regards association of Cl. welchii with other organisms may be mentioned. The 843 swabs were sent to this laboratory from the four different wards of the maternity pavilion, called in Table V, A, B, C, and D. D is the ward to which septic cases are sent. The incidence of Cl. welchii in the Ward D cases is about twice as big as in the other wards.

TABLE V.

Wards	A	B	C	D	Total
Number of swabs	117	81	296	349	843
Cl. welchii positive	5	4	11	30	50
Percentage	4·3	5	4	8.5	6

As mentioned previously and shown in Table III the percentage for the pregnant and non-pregnant women were 6.33 and 7.67 per cent respectively, which is higher than the figures obtained from the non-septic puerperal cases. There is, as has been said above, no association between Cl. welchii and group A streptococcal septicaemia. The association is with other organisms of a lesser pathogenicity. As Logan[14] has pointed out "in the majority of women uterine sepsis occurs during the puerperium, and so long as it remains local and of minor degree it is to be regarded as normal."

It is evident from the figures obtained that the incidence of Cl. welchii increases with the number of vaginal examinations and instrumentations. In this connexion it is worth recalling that medical supplies can harbour Cl. welchii. Pulvertaft[15] found sanitary pads to be a rich source of Cl. tetani and Cl. welchii. Cotton wool, according to the report of the Tetanus Committee,[16] is often infected with spore-bearing pathogenic anaerobes. Guggisberg[17] isolated the organism from gynaecological rubber bags, while there is some likelihood that Cl. welchii was introduced into the cervix of More's[18] patient with an application of radium.

It is also, however, clear, that the isolation of gas bacilli from a high vaginal swab is not, without clinical support, sufficient to cause a patient to be regarded as infected by Cl. welchii, and to be treated with antitoxic sera, sulphonamides, etc. In the absence of definite clinical signs, such a report should put the clinician on his guard, but active treatment should not be instituted without clinical evidence that invasion has taken place.

Summary and Conclusions.

Of 843 high vaginal swabs from puerperal patients showing morbidity of varying degree, 50, or 6 per cent, showed the presence of Cl. welchii. Two control series of 600 high vaginal swabs from the Antenatal Clinic and Venereal Diseases Clinic showed an incidence of Cl. welchii of 6.33 per cent and 7.67 per cent.

There was no evidence clinically that Cl. welchii had any greater pathogenic effect in these cases than the Bact. coli with which it was commonly associated. The presence of Cl. welchii in a high vaginal swab is not, without clinical evidence of invasion, sufficient to cause institution of specific treatment against the organism.

The conditions favouring the introduction of Cl. welchii are discussed.

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A Case of Osteomalacia in Pregnancy

BY

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OSTEOMALACIA, on account of the extreme deformities produced, has always been of interest to obstetricians. Litzmann,[1] when he wrote his classical monograph in 1861 on rickets and osteomalacia, regarded the latter as being an inflammatory disease of the bone. He furnished a bibliography in that article of 74 authorities, the earliest publication being early in the seventeenth century.

To-day we are chiefly indebted to Maxwell,[2, 3, 4] who describes the condition as it is encountered in China, and to Green-Armytage,[5, 6] who describes the difficulties it produces in India. From the biochemical and aetiological aspect Hannon and his Chinese co-workers[7, 8] have carried out exhaustive studies.

Acute osteomalacia is a rarity in this country and, while standard textbooks in obstetrics still continue to show pictures of deformities to be expected, the condition is seldom seen. It is therefore considered of sufficient interest to publish the details concerning a case recently encountered in the Glasgow Royal Maternity and Women's Hospital.

In this hospital the number of cases of rickets treated annually is greater than in any other one centre in the country. Hunter[13] regards the two conditions, rickets and osteomalacia, as manifestations at different ages of the same essential process. One might therefore expect that, where large numbers of bony deformities due to rickets exist, cases of osteomalacia might also be encountered from time to time, the dietetic aetiological factor being similar in both diseases This, however, is apparently not the case, for a search of the hospital records reveals that in the last 30 years there has been only one other case recorded, and it is of interest to note in passing that this case occurred in 1919, immediately following the last war. Although that case presents many features similar to the one at present under consideration, at that time there were no adequate facilities for biochemical or radiological investigation.

In the present case the patient was aged 29, and was admitted on a midwife's recommendation as an emergency suffering from antepartum haemorrhage at the 37th week of her 5th pregnancy. Her first 2 pregnancies had been normal confinements, in the years 1936 and 1938. The babies weighed 7 pounds and 7½ pounds respectively; there was no dystocia. The 3rd pregnancy ended in a 6-months miscarriage. The 4th pregnancy, in 1940, ended in a spontaneous stillbirth in the patient's home, where she was attended by the same midwife. On interviewing the midwife it was learned that, at the time of the patient's last delivery, the pelvis appeared to be somewhat contracted but, as the foetus was macerated, there was no impediment to delivery. The pelvic contraction, however, was not sufficiently marked to prevent the midwife undertaking to conduct the next confinement in

the patient's own home, which indeed she would have attempted to do had not an antepartum haemorrhage caused her to send the patient to hospital.

On admission to hospital the striking feature in the case was the extreme pain of which the patient complained in her legs and feet. Any attempt to move her limbs made her cry out. The pain in her legs was so marked as to render her quite unconcerned by the antepartum haemorrhage which was moderately severe. The adductor spasm was so great that vaginal examination to detect the cause of the haemorrhage had to be made under an anaesthetic. It was then noticed that the pelvis was markedly deformed, and that the disproportion was so great that delivery by the vaginal route was impossible. A diagnosis of acute osteomalacia was made and a Caesarean section carried out. A stillborn and partly macerated child was delivered. The bleeding had been due to mixed accidental haemorrhage.

The patient made an uneventful recovery and a further examination of her condition was carried out. A biochemical investigation of the blood showed:—

"Serum calcium = 10.1 mg. per 100 ml. Plasma inorganic phosphorus = 1.6 mg. per 100 ml. Plasma phosphatase = 7.7 Bodansky units.

"Calcium is normal; phosphorus is very low normal; phosphatase is above normal. The result is in accord with a diagnosis of osteomalacia."

A series of X-ray photographs (see Figs. 1, 2, 3, 4, 5 and 6) showed the typical deformities in the pelvis associated with this disease. There was also rarefaction of the long bones. The lucid areas encountered in osteomalacia and described by Looser[9] were present. The skull showed patchy rarefaction.

The patient's history was that she had been complaining of increasing stiffness, especially marked in the hipjoint region and in the back, over a period of 5 years. The stiffness spread gradually to her ankles, knees and wrists. During her last three pregnancies there was an exacerbation of these symptoms. In the most recent pregnancy walking was so difficult that she spent most of her time in bed. Between her pregnancies she felt very much better. She herself noticed that she was losing height and now measures 4 feet 10 inches. Her diet had been most unsatisfactory. She never drank milk; she took very few green vegetables; she did not eat bread (since "that other loaf came in"). Her food consisted chiefly of fried potatoes and meat from the ration, and occasionally fish. She stated that it was only during pregnancy that her dietary was poor, and that at such times she had a complete loss of appetite. For a year and a half she was evacuated to the country where there was an improvement in her diet and where she enjoyed better health. She returned, however, to her single apartment house in Bridgeton. It is of interest to note that in this district in Glasgow there is the highest incidence of rachitic contracted pelvis. Her husband had been unemployed for 5 years prior to the war and is at present in the Army, so that their financial position has been insufficient to provide other than an unsatisfactory diet in view of the patient's dislike of the cheaper articles in a good basic diet.

Discussion.

The Chinese workers have shown that the dietetic deficiency is of paramount importance in the production of osteomalacia. Mellanby[10, 11, 12] has proved beyond doubt that rickets is due to a dietetic deficiency. In the case just described the diet was deficient in vitamin and mineral content.

It is, however, a curious fact that osteo-

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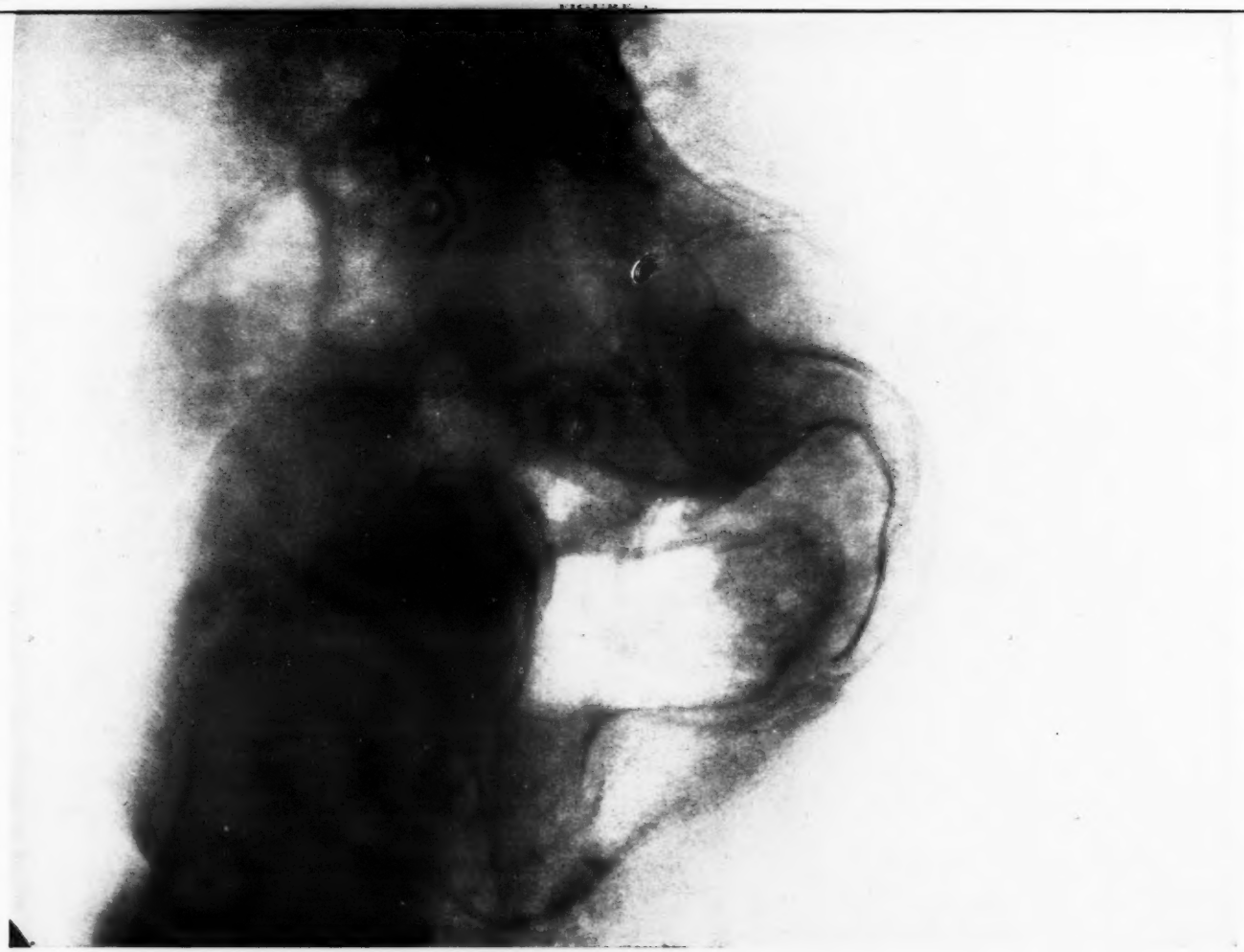

FIGURE 2.
X-ray (lateral view) showing extreme deformity of pelvis due to osteomalacia.

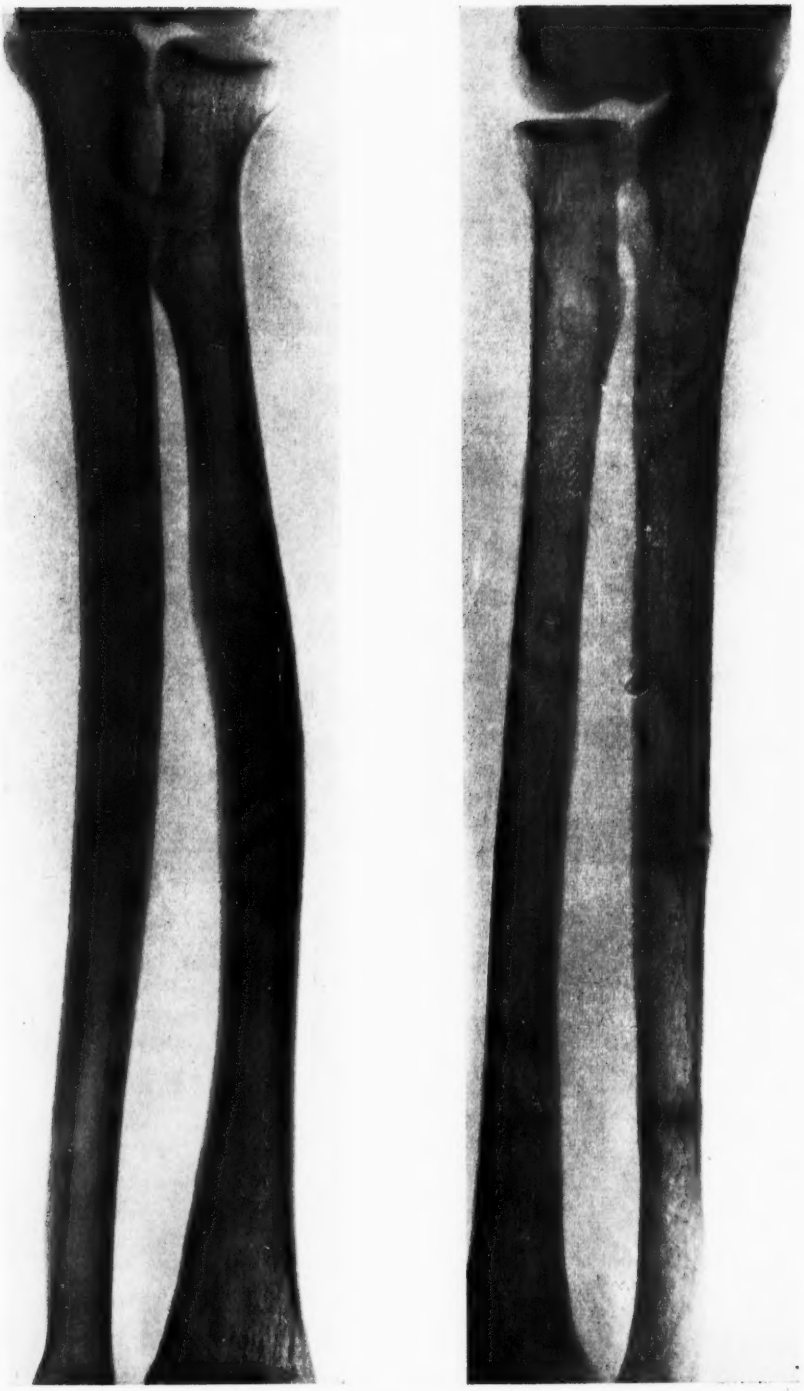

FIGURE 3.

X-ray of bones of forearm: *(right)* showing Looser's zone; *(left)* control normal forearm.
H.R.M.

FIGURE 4.

X-ray of bones of forearm: (*right*) showing rarefaction; (*left*) showing rarefaction and Looser's zone (pseudo-fracture).

FIGURE 5.
X-ray (antero-posterior view) showing rarefaction of skull.

H.R.M.

FIGURE 6.

X-ray (lateral view) showing patchy rarefaction.

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malacia should be so rare in Glasgow where rickets is relatively common, particularly if Hunter's[13] view holds good that "rickets and osteomalacia are essentially identical," or that "osteomalacia is adult rickets." The dietetic factor in the case described was pronounced, but it is not unusual to find women in this district whose dietary is equally defective without any accompanying evidence of osteomalacia. Moreover, in patients with excessive sickness of pregnancy or severe toxaemia, nutrition is often impaired without osteomalacia developing. This case, therefore, can be explained only by presupposing either that another factor in addition to faulty diet is necessary to produce osteomalacia or that mild cases of osteomalacia do in fact exist and are being missed. It is conceivable that some multiparous women in whom slight pelvic deformity is discovered for the first time in their later pregnancies may actually be suffering from a mild osteomalacia manifestation rather than the results of an old-standing rachitic deformity. Maxwell states that in China the disease often commences at puberty. Dutta[14] points out the difficulty of recognising slight osteomalacic deformity.

It would be of interest to know whether cases were of old rachitic origin or were mild manifestations of osteomalacia, for, if they were rachitic, the disease would be stationary, but if they were osteomalacic then the deformity would be progressive. This might explain why certain multiparous women, who have a good obstetric history for their earlier pregnancies, experience dystocia with their later pregnancies although apparently the weight of the baby has not increased.

Moreover, if these cases of slight pelvic contraction which are common in Glasgow were osteomalacic in origin, they would merit serious treatment with diet and vitamin D to arrest the process. This theory could be proved satisfactorily only by a radiological and biochemical investigation of a number of these cases presently diagnosed as slight rachitic pelvic contraction and this work has been already commenced. Should it prove to be well founded, the practical importance would lie in the need for further emphasis on adequate nutrition of the pregnant woman not only to prevent rickets in her offspring but to avoid bony rarefaction in herself.

I should like to record my thanks to Dr. J. C. Eaton for his biochemical investigation; to Drs. G. Jackson Wilson and Blum for their radiological examination, and to all three for their helpful comments.

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Posteclamptic Kyphosis

BY

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THE following report on 3 cases of posteclamptic deformity of the spine may be of interest.

CASE 1.

M.P. Primipara; 32 years old; from Novo Sulitza, Bessarabia; 8 weeks pregnant. Admitted to hospital unconscious, with half-hourly eclamptic fits. In spite of Stroganoff treatment the attacks ceased only on the third day after induction of labour and delivery. Three and a half weeks after the patient got up she complained of slight pain in the back, which ceased two months later. After a further two months she noticed that she was stooping. Her stoop became steadily worse, and at the same time her back began to ache in the dorsal region, especially after housework. The pain ceased if she lay down on a hard couch with her back straight.

The patient was of medium size, asthenic in build, with a decided stoop. On examination she was found to have an accentuated kyphosis of the upper and middle dorsal spines, evenly distributed. The erector spinae muscles appeared bulky and stretched, on both sides. The spinal processes of the 4th, 5th and 6th dorsal vertebrae were tender. There was excessive lumbar lordosis, and decreased mobility of the spine. X-rays taken 4 months after delivery showed that the 4th, 5th and 6th dorsal vertebrae were slightly wedge-shaped, with trapezoid flattening. The end-plates appeared crushed, especially anteriorly, where the bone was irregularly thickened. The intervertebral spaces were slightly narrowed anteriorly. The dorsal kyphosis was marked, with compensatory lordosis of the lumbar region.

CASE 2.

S.K. Second pregnancy; 24 years old; from Lipcani, Bessarabia. Admitted with albuminuria and oedema followed by eclamptic fits every half hour. Delivered by Caesarean section. The convulsions subsided slowly. Four weeks later the patient noticed that her back felt stiff when she started to walk, that she was easily tired, and that the pain in her back radiated to the abdomen. The family observed that she had begun to stoop.

On examination the physiological curves of the spine (both dorsal kyphosis and lumbar lordosis) were seen to be accentuated. The spinal processes of the 6th and 7th dorsal vertebrae were tender, and dorsal motility was reduced. X-rays showed that the bodies of the 4th to 8th dorsal vertebrae were flattened anteriorly, the 6th and 7th were wedge-shaped, the 9th had an insignificant oblique line through the upper end-plate. All the end-plates, except the lower end-plate of the 9th, were abnormally dense, together with the adjoin-

ing parts of the vertebral bodies: the bony structure was blurred. There was a slight narrowing of the anterior part of the intervertebral space between the 6th and 7th dorsal vertebrae. Kyphosis of the dorsal region was marked, with protrusion of the 6th and 7th vertebrae.

Treatment: Both these cases were treated in hyperextension in plaster of Paris, with physical exercises. When the plaster was removed after 12 weeks the first case showed only slightly improved posture, the second case considerable improvement. They now wear only a linen corset as support, and during the whole period of observation have been free from pain.

Case 3.

R.M. Primipara; 18 years old; from Jerusalem. Previously always in good health. Four days before admission felt very ill, with oedema and albuminuria. On admission, clonic convulsions occurred, each lasting about 2 minutes. As the attacks became worse, and in view of her general condition, Caesarean section was performed and a live child delivered. Three hours after operation the attacks recurred. Lumbar puncture did not show increased pressure in the cerebrospinal fluid. The attacks continued, and the patient died 8 hours after the operation.

Postmortem examination revealed only slight changes in the internal organs. The parathyroid, suprarenal and all other glands were normal. The cartilage of the 1st lumbar vertebra was torn and the upper end-plate fractured irregularly. The intervertebral disc between the 12th thoracic and 1st lumbar vertebrae was prolapsed. Histological examination showed a large zone of fibrous transformation of the marrow in the 1st lumbar vertebra, with secondary cartilage formation and increased vascularity. X-rays confirmed a compression fracture of the 1st lumbar vertebra, with traumatic prolapse of the intervertebral disc.

Discussion.

Experiments with 3 white rats injected with 1,500 units of tetanus toxin were interesting. Tonic-clonic contractions occurred in all three on the third day after injection, lasting with intervals for about 34 hours. Two rats died after progressive paralysis, but the third recovered from the paralysis after 4 days, and was given a second injection of 2,500 units, dying 4½ days later. X-rays of the first 2 rats showed no changes in the vertebrae; but X-rays and autopsy of the third rat showed a compression fracture of the 2nd lumbar vertebra, with anterior flattening.

Possibly some useful anatomical and mechanical assumptions can be made from the evidence provided by these 3 cases. The vertebral column protects the spinal cord, and its snake-like curve is important because it enables it to take without damage far greater strain than a straight column could support. The muscles which influence flexion and extension of the vertebral column are co-ordinated. All the extensors (except perhaps posterior serratus, superior and inferior) bend the spine backwards, but are weaker in the dorsal region than in the lumbar and cervical (Fick). The flexors form a muscle chain from sternomastoid, which bends the head, to iliopsoas, which increases the lumbar lordosis. Mobility in the dorsal region is limited to 90 degrees of flexion and 40 degrees of extension, so that the flexors gain a mechanical advantage. This may explain the changes in the anterior part of the vertebra after convulsions. Then, the abruptness of the strain on the vertebrae is an important factor, as the margin of elasticity is exceeded with relatively little applied

force, especially when, as in convulsions, blow succeeds blow in quick succession. Every new blow will deform a vertebra already made rigid by a force which has exceeded the limit of elasticity, and the result can only be a fracture. This may be a major fracture, or merely a crushed trabecula, but in the latter case a slow sinking of the vertebral body will result, with increasing kyphosis. The anterior part of the affected vertebrae is flattened, leaving them wedge-shaped or trapezoid. The end-plates are thickened, together with the adjoining spongiosa of the vertebral body, which becomes irregularly dense, especially anteriorly.

Differential diagnosis. (Only the commoner conditions are mentioned.)

1. Deformity due to convulsion-therapy or tetanus. Similar to the post-eclamptic.

2. Adolescent dorsal kyphosis. Located lower in the dorsal section, with the centre of deformity in the 8th and 9th vertebral bodies. Changes are also found in the vertebral discs (node of Schmorl).

3. Senile kyphosis. Atrophy, enlargement of intervertebral spaces, and fishlike vertebrae.

4. Osteomalacia. General clinical symptoms. Atrophy of the vertebral bodies, and enlargement of intervertebral spaces.

5. Spinal tuberculosis. Stiffness of the affected part of the spine and, later, gibbus. Irregular intervertebral spaces. Cold abscesses.

Summary.

Three cases with post-eclamptic changes in the spine are reported. All were in good health prior to pregnancy. Two showed changes of the dorsal region similar to those described after tetanus and convulsion-therapy; the third showed a traumatic disc rupture with compression fracture of the 1st lumbar vertebra.

It is suggested that these changes, due to abrupt and recurring muscle contractions acting on the bones, exceed the limit of elasticity and finally cause a split of the trabeculae, with an accentuated dorsal kyphosis or a fracture proper.

From the therapeutic point of view we recommend examination of the spine in cases of eclampsia before they leave hospital and again after 4 weeks. If spinal changes are present a plaster of paris corset should be applied for about 12 weeks, and suitable physical exercises should be given. This treatment ought to prevent secondary deformities. Finally, the tendency to calcium deficiency in pregnancy should be remembered and this shortage should be met by calcium administration.

The Hogben Pregnancy Test with a Note on the Breeding of Xenopus for the Test

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AND

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INTRODUCTION.

THE South African clawed toad *Xenopus* Laevis was first introduced as an assay animal by Hogben[1] in 1930. Since then much work has been done on the uses, husbandry and breeding of these toads. It is now well established that they can be used as a reliable test animal for pregnancy diagnosis in humans, and assay of melanophore-expanding hormone. There are many other possible uses for this toad which are being explored. Wartime conditions make it difficult to import the animals from South Africa but we can prescribe a method for breeding and rearing them in the laboratory.

This toad has many great advantages over other test animals. It lives indefinitely in the laboratory—we have kept them for over 12 years and they still respond to injection of gonadotropic extracts by ovulation and extrusion of ripe eggs. Recognition of this response does not involve killing the animal, which can be used repeatedly. This depends on the fact that *Xenopus* does not ovulate spontaneously under normal laboratory conditions and does not extrude all its ripe eggs simultaneously after an injection of gonadotropic extract. Only for the last 2 years have we kept continuous records to show the number of times the same animal can be used. Figures obtained in this period show that each toad can be used over 20 times (see p. 5). The animal can be kept in good condition without excessive demand on laboratory routine—they need feeding and cleaning only once a week and can survive 6 month's starvation if necessary. The normal animal in good condition ovulates and extrudes ripe eggs into the water within 6 to 18 hours after a *single* sufficient dose of gonadotropic substance.

Ovulation of *Xenopus* after injection of anterior lobe extract was first demonstrated by Hogben in 1930. In 1933 Bellerby[2] showed that the animal can be transported from South Africa to Europe and kept in suitable condition for use as a test animal for pituitary extracts.

Shapiro and Zwarenstein[3] reported that *Xenopus* cannot be kept in captivity for any length of time without adverse gonadic changes to which they have given the name 'captivity effect.' These workers claim that 'the ovaries of captive females were severely atrophied after 6 months' captivity . . . despite regular feeding and change of water.' If established, the existence of such an effect would seriously detract

from the practical utility of *Xenopus* as a test animal outside South Africa. After a series of investigations planned to test Shapiro and Zwarenstein's claim, Alexander and Bellerby[4] showed that the development of the ovary depends directly upon the amount of food consumed, and that atrophic changes do not develop in the ovary if the animals are adequately fed. Further work was undertaken to ascertain the optimum conditions under which the toads should be kept (Landgrebe[5]). This showed that (*a*) overcrowding leads to pollution of the water, diminished food intake and retrogressive changes in the ovary, (*b*) if the animals are not overcrowded, weekly feeding suffices to maintain them in a satisfactory condition, (*c*) the toads should be kept at a temperature around 22°C.

Shapiro and Zwarenstein,[3, 6, 7] Bellerby,[8] Landgrebe,[5] Elkan,[9] Crew,[10] and Scott,[11] have now independently obtained sufficiently extensive records to justify the claim that ovulation of *Xenopus* can be used as a test for the gonadotropic substance in pregnancy urine. Landgrebe collaborated with Crew's pregnancy diagnosis laboratory in a comparative study of the Aschheim-Zondek and of the *Xenopus* test; 279 cases tested by both methods showed 6 discrepancies, 5 specimens gave negative *Xenopus* and positive Aschheim-Zondek results. Four of these 5 were done in early pregnancy and further concentration of the urine might have given more concordant results. One specimen gave a positive *Xenopus* and a negative Aschheim-Zondek but clinical confirmation was not obtained so that we cannot decide which was correct. The Aschheim-Zondek test is not considered infallible. Robson[12] claims 1 to 2 per cent inaccuracy for it.

Crew proposes that the test using *Xenopus* be called the Hogben Test, in conformity with the nomenclature of others of its kind. Crew precipitated the activity from the crude urine by the addition of acetone and claims that the Hogben test can at once replace the Friedman for rapid assay, but suggests that it is not quite so reliable as the Aschheim-Zondek. Scott has evolved a new and better technique for concentration of the urine. Scott found that "Urines from 1,000 cases in which pregnancy diagnosis was required have been examined by the new process using the Friedman and Hogben tests simultaneously, the results of all cases being in complete agreement and confirmed by the subsequent clinical condition of the patient." No toads died during the course of Scott's investigation. Scott's extraction technique is rapid and simple and has been in use in this Medical School for 2 years.

The present communication deals with the results obtained in routine tests for cases in which clinical diagnosis was doubtful, and describes the method in detail.

Animal Husbandry.

We keep *Xenopus* in metal tanks 24 by 15 and 12 inches deep, stove-enamelled black inside and fitted with a wire mesh lid. An overflow pipe is fitted so that the water is at a depth of 6 inches. Such tanks hold 20 toads of the usual size (50g.) without overcrowding. Eight of these tanks are kept in a small room thermostated at about 22°C. A trickle of tap water flows through each tank. Toads are fed once a week with fresh raw liver cut into cubes of about 0.5 cm. side. The day after feeding excess food is removed from each tank with a net. The tanks are labelled A+, A−, B+, B−, C+, C−, D+, D−. Toads from tanks A are used only during the first week of each month and are replaced in those tanks at the end of the week, those which ovulate into A+ and the others into A−. Toads from tanks B are used only during the second week of each month and so on. This

ensures that at least 3 weeks elapses between ovulations.

Concentration of Urine.

The specimen of urine is first concentrated by Scott's method:

To 100 c.c. of urine in a 250 c.c. graduated cylinder, add 100 c.c. of water. Add 1 c.c. of brom-phenol blue indicator and adjust to *p*H 4.0 by addition of 20 per cent hydrochloric acid, adding about 0.25 c.c. of acid at a time, with constant shaking until the colour changes from deep blue to a point where the blue almost disappears. 10 c.c. of well-shaken suspension of kaolin (20 per cent aqueous suspension B.D.H. kaolin washed with acid) is added and the urine thoroughly mixed by inversion several times. Allow the kaolin to settle to a layer below the 30 c.c. mark. Pour off the supernatant fluid and centrifuge the kaolin suspension. Decant the supernatant fluid and thoroughly stir the kaolin with 10 c.c. of N/10 NaOH. Stand the mixture for a few minutes and then centrifuge. Decant the supernatant fluid into another tube, neutralize it by the addition of about 0.75 c.c. 10 per cent HCl and add about 1 gram of solid glucose. Dissolve the glucose and the extract is ready for immediate injection or is stable for several weeks if kept in a refrigerator. For further details see Scott's paper.

Test Animals.

Only animals which have previously ovulated after injection of gonadotropic extract are used. Toads in use for the first time may be 'primed' 3 weeks before use by the injection of 100 I.U. chorionic gonadotropin. Test jars (2 pound jam jars) are fitted with a piece of enamelled wire netting at the bottom so that any eggs extruded fall through the netting, and the occasional eating of the eggs by the toad is avoided. The jars are half filled with water and are fitted with a wire-netting lid. It is advisable to stabilize the temperature of the test jars at 22°C. though this may be slowly* raised as high as 30°C. if a more rapid result is required. Temperature has little effect on sensitivity but an increase from 21°C. to 31°C. decreases the average time between stimulus and response from 18 to 9 hours.

Scott used 4 toads per test and injected them intraperitoneally. We started by using 3 toads per test and, as we found intraperitoneal injection dangerous, we injected the urine extract into the dorsal lymph sac. More recently it has been found that 2 toads are sufficient for each test provided that they have been kept for some time under the conditions outlined above. In this case only 50 c.c. of urine is concentrated into about 5 c.c. of extract. Thus 100 toads, at a cost of only two or three shillings per week for food, will suffice for over 500 tests per annum.

Performance of Test.

One toad is taken from the positive and one from the negative tank corresponding to the week of the month. What little evidence we have suggests that the animals from the negative tanks are slightly more sensitive than those from the positive. This suggests that, for maximal sensitivity, 3 weeks is not a sufficiently long period between ovulations. Each toad is injected with 2½ c.c. of extract into the dorsal lymph sac and each is placed into a test jar. A

* The temperature of the toads should never be changed suddenly except by a few degrees—*Xenopus* maintained at 22°C. for long periods do not always survive a *sudden* change of 10°C. If gradually acclimatized these toads will survive temperatures from 1°C. to 33°C. but will not eat below 12°C.

positive reaction is denoted by the appearance in the test jar of ova, 5 to 30 hours after injection according to the temperature of the test. Usually hundreds of eggs are extruded, and if only a few are found the test must be considered a weak positive.

Results.

Though the test has given correct positive results as early as 4 days after the first missed period, we find that negative results from such early cases are not reliable. We have therefore confined our tests to cases at least 10 days after the first missed period. Most of the cases were from the Aberdeen Maternity Hospital and Royal Infirmary, but some were from local general practitioners and from military hospitals. From the latter sources ultimate clinical findings were not always obtained.

No. of toads per test	No. of tests	Result of test	Clinical check		No reply
			Correct	Incorrect	
3	78	+	64	0	14
3	62	—	59	0	3
2	70	+	53	0	17
2	48	—	42	2	4

So that of a total of 258 tests, 220 were checked against ultimate clinical findings and 218 were found correct. Most of the positive tests where no reply was obtained, were from Service cases.

One incorrect negative was from a patient aged 41, who at the date of the test had an amenorrhoea of 3 months and had been suffering from flushings for many months. She was extremely stout and the uterus was not palpable. Six weeks later pelvic examination showed that the uterus corresponded to 4 or 5 months' pregnancy.

The other incorrect negative was from an extremely obese patient, aged 49, who had 3 months' amenorrhoea and was complaining of severe flushings and other menopausal symptoms. The first test done was negative. Three months later another test was strongly positive and the menopausal symptoms had disappeared.

It would seem that the test is not reliable in patients showing menopausal symptoms. It would be advisable in these cases to repeat the test a few times so that fluctuations in hormone output might be overcome.

Incidentally, the degree of the reaction, especially on repeated tests, has a certain prognostic value in case of threatened abortion. On several occasions, of patients with identical histories and clinical findings, some went to full term when the test was strongly positive, and some aborted within a few days when the test was negative or weakly positive. As illustration, histories of a few patients on whom repeat tests were made are outlined:

Case 1.

Mrs. O. Two previous spontaneous miscarriages. L.M.P. August 15th, 1942. Brisk haemorrhage on October 18th, 1942, only. First test October 20th, 1942, weak positive. Slight bleeding November 2nd to 7th, 1942. Second test November 7th, 1942, negative. Aborted November 10th, 1942.

Case 2.

Mrs. C. First pregnancy. L.M.P. April 2nd, 1942. First test, June 2nd, 1942, weak positive. Started slight haemorrhage, June 6th, 1942. Treated as threatened abortion. Slight haemorrhage, July 8th, 1942. Second test, July 11th, 1942, strong positive. Bleeding getting gradually worse. Third test, July 27th, 1942, weak positive. Increased bleeding and pain. Fourth test, August 6th, 1942, very weak positive. Aborted August 16th, 1942 (fresh foetus of about 4 months).

Case 3.

Mrs. T. Fair amount of bleeding after 3 months' amenorrhoea. Clinically, 'inevitable abortion' Test, strong positive. Went to full term.

Case 4.

Mrs. P. Five months' amenorrhoea. Query

missed abortion. Test, weak positive. Aborted 9 days later. Live foetus.

CASE 5.

Mrs. Th. Previously missed abortion retained for 4 months. L.M.P., May 18th, 1943. Slight bleeding, September 15th, 1943. Hyperemesis and 'breast changes' disappeared first week of September. First test, September 21st, 1943, negative (one toad). Second test, September 24th, 1943, weakly positive. Treatment as threatened abortion. No further bleeding, breast changes reappearing. Third test, September 29th, 1943, positive. No further symptoms of threatened abortion, size of uterus corresponding to 4 months' pregnant. Further progress undisturbed.

All the tests recorded in this paper were done on the same group of 32 toads, and we can calculate the number of times each animal was used. There are 140 three toad tests and 118 two toad tests, i.e., a total of 656 toad injections. Previous to the tests recorded here, a total of 119 toad injections were made in preliminary experiments using different methods of extraction. That is, a total of 775 injections into 32 animals, i.e., each toad has been used 24 times and they all are still responding satisfactorily. No toad died as a result of these tests.

BREEDING OF XENOPUS IN THE LABORATORY.

A preliminary communication on the breeding of *Xenopus* was published 2 years ago (Landgrebe & Purser[13]). We have since bred nearly 100 toads and have found them suitable for pregnancy diagnosis and capable of producing a second generation.

Fertilized eggs of *Xenopus* can be obtained at any time of the year if a male is induced to couple an ovulating female in pond or in glass-distilled water (not in present day tap-water or in water containing traces of copper).

A male and a female toad, both in good condition, are placed in pond water at 18 to 25°C. in a flat-bottomed dish. Both are injected with a gonadotropic extract, 50 to 100 I.U. chorionic for the female, 10 to 20 for the male. Coupling usually occurs within 24 hours and up to 10,000 fertilized eggs may be collected from the dish after about 48 hours. If the toads are in excellent condition about 99 per cent of the eggs laid are fertilized. Otherwise, only a few hundred may be laid and only a few of these fertilized. Animals that have been made to ovulate every few weeks for pregnancy diagnosis are not suitable, they should first be given a few months' rest under good conditions.

Sometimes the male requires longer than 24 hours for the extract to have the desired effect, and it is often advisable to inject the male the day before the female. If the male shows secondary sexual characters (black 'gloving' of the fore-limbs), an injection is not usually necessary.

When first laid the eggs are half black and half white and after a few days fertilized eggs can easily be visually detected. They become brownish in colour with a cleft or dark line across them. They should be separated from the unfertilized eggs which either remain half white, half black, or go completely white.

At this stage the fertilized eggs can be moved with a pipette without danger. They are carefully separated and placed in shallow pond water at a temperature from 18°C. to 25°C. The tadpoles hatch out in a few days and should not be moved or handled in any way until they have metamorphozed. An aquarium 12 inches by 12 inches by 8 inches deep, containing water to a depth of about 6 inches is large enough for about 50 tadpoles. The tadpoles grow quite fast if enough food is available. For this reason it is better to start in the spring or early summer, when a maximum amount of food is present in pond water and the

bottom deposit. Also more daylight will then be available to keep the food supply cultured during the few months that the tadpoles grow. *Xenopus* tadpoles, unlike *Rana* tadpoles, can eat only free-living or suspended green algae, and we find a growing culture of *Chlamydomona* suitable.* This can easily be cultured in the laboratory if large supplies of natural pond water are not easily available.

A small handful of hay is boiled in a bucketful of tap water (if the water is fed through copper pipes the tap should be turned full on for a few minutes before taking the bucketful). After cooling, the water is decanted into a glass aquarium placed so as to receive as much daylight as possible. The infusion is inoculated with *Chlamydomona* or a little pond water. The culture forms a heavy green layer at the bottom after a few weeks. Some of this can be added daily to the tanks containing the tadpoles.

After about 10 weeks some of the tadpoles are metamorphosing while others (about 60 per cent) will have grown very little. We feed these small animals to the young *Xenopus* when first metamorphosed.

About a week after metamorphosis, the young toads are transferred to another similar aquarium, otherwise they will eat even the larger tadpoles. The larger toads will also eat smaller toads so that very small adults must be kept separate. The young *Xenopus* are fed on very small pieces of liver or on any live food available. Live food is taken more readily than liver and the aquaria require less cleaning. We have produced a 25 gram female in 8 months by feeding on live *Lebistes*, while on a liver diet they rarely exceed 10 grams in this time. It is not practicable to culture *Lebistes* to supply food to the adults, but other small animals such as *Gammarus* might be worth investigating.

From this *Lebistes* fed female, and a laboratory bred male, we have obtained fertilized eggs and have reared these to the stage of 16 gram females which ovulate after injection of chorionic gonadotropin. With such small animals, however, a concentrated extract must be used to keep the volume of injected fluid low. For pregnancy diagnosis the animals should be at least 30 grams in weight. The main point in recording these results is to show that laboratory bred animals are fertile and respond to chorionic gonadotropin, and that their progeny also respond to pregnancy urine extracts.

Conclusions.

The Hogben test for pregnancy using the Scott technique for extraction of the urine is as reliable as any other test provided that at least 10 days elapse since the first missed period.

Menopausal urines extracted by precipitation techniques often give a positive Hogben test in the absence of pregnancy (Landgrebe 1939), but with the Scott extraction method the test gives a negative result in these cases and also gave a negative in the case of two pregnant patients showing menopausal symptoms at the time of the test.

The Hogben test is more rapid and requires much smaller demands on laboratory routine than other tests. At 22°C. a

* In a private communication from Dr. A. S. Parkes we learn that Dr. R. Deanesly has been successful in rearing the tadpoles on a diet of dried liver. The authors have tried a diet of raw liver suspension without success. Dr. Parkes says: " the liver is ground up with a little flour and dried as a thin layer spread on glass sheets. When dry it is ground up in a coffee mill so that it will pass a 30-mesh sieve. With a tadpole density of about 5 per litre we find that 2 to 3 mg. of dried liver per tadpole gives good growth so that a considerable proportion complete metamorphosis in under 8 weeks."

result is obtained within 18 hours and the animals require feeding and cleaning only once a week. Apart from these advantages the test is much less expensive than the Friedman or the Aschheim-Zondek in both food and animal costs. One hundred toads can be fed for 2 or 3 shillings a week and will suffice for over 500 tests per annum. Each toad under pre-war conditions costs about ninepence to import and can be used over 24 times.

SUMMARY.

1. Two hundred and fifty-eight tests for pregnancy, using the Scott technique for extraction of urine, were undertaken in cases in which clinical diagnosis was doubtful.

2. Two hundred and twenty have been checked against ultimate clinical finding and, except in 2 cases where the patient showed menopausal symptoms, were found correct.

3. Two toads are sufficient for each test if they are in good condition.

4. Each toad was used over 24 times and still responds satisfactorily.

5. Laboratory-bred *Xenopus* can be used for the test and are capable of producing a second generation which will also respond to pregnancy urine extracts.

6. The Hogben test can be carried out at a fraction of the cost, is more rapid than, and is at least as reliable as, the Friedman and the Aschheim-Zondek tests.

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Trichlorethylene and Midwifery

BY

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FOLLOWING a suggestion made by Dr. John Elam, in this journal, I have made an investigation into the possibilities of trichlorethylene as an analgesic in labour. It was hoped to find an agent which would be safe in the hands of midwives and which would, at the same time, provide relief during the actual delivery. While no attempt is intended to decry or replace Minnitt's and other gas and air machines, it must be admitted that completely painless delivery by this means is exceptional. The requirements kept in mind were, accordingly:

(1) Absolute maternal and foetal safety.

(2) Simplicity of apparatus and administration.

(3) Complete analgesia for the parturient.

(4) Cheapness in first and subsequent costs.

APPARATUS.

The first apparatus was improvised in a few minutes, and could be again by anyone wishing to try the method. The concertina rubber tube is disconnected from a standard Boyle's Gas-Oxygen machine complete with facepiece and three-way gas-cock. The free end of the tube fits nicely over one neck of a 16 ounce Woolf's bottle. A piece of standard rubber drainage tube is inserted into the other neck of the bottle so as to fit closely and reach to about 2 inches from the bottom. It is then cut off flush with the neck, the natural curve of the tubing being allowed to direct it to the centre. The mask must be of the inflatable rim type and in good condition. In the absence of positive pressure from gas cylinders, etc., the amount of the drug inspired depends entirely upon the gas-tight fit of the mask. The preparation used was "Trilene" (I.C.I.) and one ounce poured into the bottle makes the apparatus ready for use. The three-way tap is kept permanently in the "Valves" position so that the patient inspires over the trilene and expires into the air. To make the apparatus fool-proof, a special gas-cock was later designed and made for me by A. Charles King, Limited. With this, the tap position cannot be varied and the valves are of a special low inertia type. The cost of the apparatus, using new parts throughout, would be about 50/-, which compares rather ludicrously with that of any other machine. In addition to the above, a small wooden box in which to stand the Woolf's bottle to prevent its being knocked over can be used if desired.

METHODS OF USE.

The word "technique" seems ponderous when applied to the following simple procedure.

(i) The mask is applied to the face when the accoucheur would ordinarily say "Stop pushing." Further instructions relate to the obstetrical position rather than to the

analgesia. Thus: "Breathe in and out quickly," when a contraction threatens over-rapid delivery, or "Push" when advance is required. The patient co-operates almost consciously although reaction time is a little prolonged and the instructions should be simply and loudly stated.

(ii) The last few pains can be anaesthetized, and sometimes the voluntary efforts bettered, if the mask is applied as a contraction begins and the patient is instructed to push. The mask is removed between pains until the time arrives to employ Method (i).

(iii) The mask is applied, and when the patient has had a few seconds to become accustomed to the smell, she is told to breathe in and out deeply. After 12 to 16 such excursions she may still be able to answer questions (e.g. "Can you still smell it?") but will tolerate such operations as episiotomy, perineal suture, low forceps (see "c" below), and, incidentally, incision of whitlows, removal of fingernails, and other minor surgical procedures.

In connexion with the above, the following points need emphasis: (*a*) The drug definitely increases the time between uterine contractions, so that birth of shoulders and trunk may require to be assisted by fundal pressure in order to avoid asphyxia in the child from compression of the thorax in the vagina. If this is done no child will give any anxiety. (*b*) After removal of the mask, the patient is disorientated for a very short time, and during this time she needs to be reassured. This is specially important in Method (ii). Because of this and the interference with contractions, probably Method (ii) should not be practised except by a doctor. (*c*) The patients often move, the commonest motion being extension of the knee joints. It is noteworthy that these movements are not of the trunk or of the "operation area," and do not interfere with delivery. In forceps cases, however, if heel-type lithotomy supports are used, this extension of the knees moves the trunk up the bed, making the operation impossible. If knee crutches are used, however, the delivery can be easily accomplished. (It may be worth while to point out here that this use of the apparatus was an incidental finding, and not that for which it was intended.)

Results.

About 80 cases have been supervised by me personally, and a further series by ex-colleagues who have continued the method at Sharoe Green Hospital, and have sent me their results. Some of my cases are from this hospital and others from Stepping Hill. My thanks are due to both Medical Superintendents for permission to publish the results. No case has been delivered without medical supervision, though in several cases the supervision has been somewhat remote.

Case 1.

Primigravida, aged 19. Method (i) was used. The patient co-operated normally and sustained a trifling 1st degree tear. As this occurred she called "you're hurting me." The child cried immediately and the mother recovered to normality in 5 to 6 breaths. She would admit to no after-effects at all, even in response to leading questions. She had not even a bad taste in the mouth. On inspection of the bottle no Trilene seemed to have been used. The obvious conclusion was drawn that the method was useless. To our surprise, however, the girl declared that she remembered nothing after seeing me and had felt no pain. She had no recollection of saying she was being hurt and had not, in fact, been hurt. When questioned again the following day, she said she had had gas for teeth and much preferred this agent because of the absence of after-effects. After this she "ate a good dinner" within half-an-hour. Enquiry revealed that this was so. A nurse, unable to tell from her condition that she had had an anaesthetic, gave her the normal meal, which she accepted and ate without demur.

SUMMARY OF SUBSEQUENT RESULTS.

Analgesia was complete in every case. All patients were amnesic. Some had short retrograde amnesia and were bewildered at finding delivery completed, having no recollection of the application of the mask. Most patients seemed to respond to instructions unless the administration exceeded about 20 minutes, after which consciousness was lost. Even in these patients consciousness was restored in 6 minutes or less. All were disorientated for periods varying up to 10 minutes, although this could be reduced by talking to the patient. All patients were able to change position in bed, after separation of the child, without assistance. The maximal amount of trilene used was about 3 drachms, though most cases (Method i) required only ½ to 1 drachm.

Side effects. The tachypnoea and cardiac arrhythmia said to be associated with this drug were not observed in any case, in spite of close observation with this in mind.

After effects. All mothers were questioned on this point immediately and again on the following day. Leading questions were used, e.g. "Sick?" "Dizzy?" "Bad taste in mouth?" "Headache?" Many patients grew mildly impatient of this catechism and said "No, doctor, I feel grand." One patient in the whole series vomited and she had vomited several times before (48 hours labour). No other patient had any after-effect. All were offered tea immediately after delivery in the usual way, and none refused because of the anaesthetic. One ate chocolate instead. Several patients produced cosmetics and made themselves presentable within an hour of delivery.

Effect on uterine contractions. Using Method (i), this did not arise. Using Method (ii), frequency seemed to be diminished in almost every case as stated above.

Maternal disease. The series was quite unselected. The only criterion was whether or not a doctor was able to be present. Accordingly included are 4 cases of mitral stenosis, 3 of less definite cardiac lesions and 9 of pre-eclamptic toxaemia. Three of the latter were of such severity that premature labour had been induced. These complications did not seem to constitute contra-indications.

Obstetrical abnormalities. Four breech deliveries are included, in one of which extended arms had to be brought down by manipulation. This was easily accomplished. Possibly Method (ii) was seen at its best in breech delivery. Delivery by the forceps cases numbered 4, but are not stressed as this was not the purpose of the investigation. A colleague remarked that it was "an ideal anaesthetic from the operator's point of view." Perineal tears were certainly no worse than usual, and a labour ward sister volunteered the opinion that tears under this analgesia were less frequent than usual, and suggested that relaxation of the perineum occurred. (Praise indeed!)

Effects on the infant. If anything, the onset of respiration appeared to be accelerated. Probably the effect was nil, although the possibility of asphyxia from compression of the thorax in the vagina owing to delay of the next pain after delivery of the head has been mentioned.

Patients' opinions. As stated all patients were questioned twice. All except one were enthusiastic. One multipara agreed that she had had pain previously, and none this time, but stoutly maintained that she preferred things "natural." All patients who had had previous anaesthetics, contrasted the absence of after-effects in this method. One patient had had gas and air before "but it were no good. This were grand." The most gratifying comment was that of a woman who joined in when her neighbour

was being questioned: "We all like that gas stuff—it's grand."

Summary.

An investigation into the use of trichlorethylene in midwifery has been made. The results are encouraging, and suggest that painless delivery could be brought within reach of more women. A short addition to the gas-air course might make this method available to unsupervised midwives. The simple apparatus described can readily be improvised, so that anyone wishing to try the method can do so immediately. Possibly a large number of cases could quickly be collected by this means. A. Charles King, Ltd., can supply the special valve if required. The apparatus is cheap and portable and readily available for domiciliary use.

Since the completion of this report, the excellent contribution by Dr. A. Freedman has appeared in the *Lancet*. He has used a different inhaler which appears to give a weaker vapour. This possibly accounts for the absence of effect on uterine contractions and also for the 6 failures recorded. Apart from this, his observations accord fairly well with the above.

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Amyoplasia Congenita Causing Malpresentation of the Foetus

BY

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FOETAL abnormality is numbered among the causes of malpresentation, but fortunately amyoplasia congenita is rarely seen. This condition which has been of interest chiefly to the pediatrists or orthopaedic surgeons who are responsible for the treatment of the deformed infant, becomes the concern of the obstetrician when causing complications during labour. Hence it has been considered worth while to report the following case.

Mrs. S. attended the antenatal clinic from the 28th week of pregnancy. She was a third para, aged 31, with the following obstetric history:

First child, weighing 9 pounds, stillborn after instrumental delivery.

Second confinement $4\frac{1}{2}$ years ago, a living child weighing $7\frac{1}{2}$ pounds, delivered by the forceps.

In the early weeks of the pregnancy under consideration sickness occurred, also flushing and faintness. Routine treatment was given at the clinic, and the patient's general condition improved.

Twice between the 36th and 38th weeks version without an anaesthetic converted a breech presentation to a vertex. Version was very easy as there was a considerable degree of hydramnios.

Admitted to hospital on May 5th having vague pains with the foetus presenting by the vertex, abnormality was not suspected until 18 hours later when the membranes ruptured and the foetus was found to be in the transverse position. It was impossible to push the vertex over the brim, but manipulation to a breech was easy. A binder was applied but uterine contractions did not improve, and on re-examination after $5\frac{1}{2}$ hours the foetus was again transverse. Manipulation again resulted in a breech. The binder was re-applied and an X-ray taken. The plate showed the foetus in the right sacro-anterior position with thighs and knees flexed, but the outline of the limbs was indistinct owing to the blurring effect of hydramnios. After re-manipulation, labour progressed more rapidly and in 9 hours the buttocks and right foot were presenting at the vulva. The left leg, which was extended, was easily brought down and the next contraction expelled the body to the umbilicus. By this time the deformity of the lower limbs was obvious. Both arms were on the chest and were drawn down to prevent extension. The head, a tight fit in the pelvis, was delivered by combined traction and fundal pressure, chloroform being administered during these manipulations.

The 3rd stage of labour was completed in 15 minutes, free loss following expulsion of the placenta.

A first degree tear of the perineum was repaired with two silkworm gut sutures. The puerperium was normal with the exception of a rise of temperature to 99°F. on the 4th evening when the breasts were filling. Pathogenic organisms were not found in a vaginal swab taken the next day.

The child, a female weighing 6 pounds, was a typical example of amyoplasia congenita as seen in the illustration. There

Anterior view showing facial abnormality.

M.I.E.

Anterior view of amyoplasic infant showing contraction of joints.

M.I.E.

Posterior view showing talipes.

M.I.E.

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was a spastic deformity of the upper and lower limbs. Movement was limited in all directions at the shoulders, elbows and wrists. The elbows were semi-flexed as were the wrists; the hands, with their long claw-like fingers being pronated. The thighs and knees were also in semi-flexion and there was a severe bilateral talipes equinovarus. The facial lesion was very interesting, there being rigidity of the tempero-maxillary joint making it impossible for the mouth to be closed completely, a factor of difficulty where feeding was concerned. X-rays failed to reveal any bony lesion. The skin was dry and scaly resembling a case of ichthyosis. This is well shown in the photographs.

Discussion.

Amyoplasia congenita is a condition of unknown aetiology, characterized by congenital symmetrical joint rigidities of varying degree unassociated with inflammatory change.

Sheldon[1] expressed the view that the initial defect consists of a developmental aplasia of certain groups of muscles. Following upon the aplasia of muscle, secondary developmental changes occur in and around the joints, leading to the classical picture of fibrous ankylosis.

Stopford Price[2] gives a record of the finding at autopsy on a case dying from intussuception. The joint changes were such as could be accounted for by the fact that flexion had never occurred *in utero*. Besides the non-development of the full articular surfaces, certain fibrous bands and ligaments which developed around the joint also contributed towards limiting flexion.

Considerable work has been done on the condition by Middleton[3] who quotes a case in which there was apparent involvement of musculature of the trunk, but I have been unable to find a reference in literature to affection of the facial muscles as in the case under consideration.

Working on the pathology of the condition, Middleton found the affected muscles represented by aggregations of fat with a core of muscle fibres. He writes, "I am inclined to look upon this condition, in fact upon all muscular dystrophies, as examples of congenital anomaly of muscular development, whereby the muscle cells are deprived of those factors which normally enable them to maintain themselves in a highly differentiated condition."

No specific pathological change has been detected in the central nervous system. Neither trophic nor sensory changes occur. The joint rigidities make tendon reflexes difficult or impossible to obtain.

Usually the mental condition of the afflicted child is normal, though Cook[4] reported a case of mongolism associated with amyoplasia in a child aged $7\frac{1}{2}$ years.

Cases with fixed extension of the elbows and pronation of the forearms with flexion of the wrists bear a resemblance to Erb's type of brachial palsy, but in the latter condition the arms are flailed and there is no fixity of the joints.

It is interesting to note that a similar condition is found in lambs, frequently associated with hydramnios or oligoamnios. Usually the deformed lamb is stillborn, probably due to abnormality of the respiratory muscles. It has been possible in breeding from experimental herds to reproduce the condition in successive generations.

Comment.

In the case under consideration, repeated malposition of the foetus in the last 4 weeks of pregnancy, and also during labour, resulted from the spastic condition of the foetal joints. Amyoplasia prevented the

child maintaining a normal position *in utero*.

Hydramnios, a common concomitant of foetal abnormality, prevented pre-natal X-ray diagnosis of the deformity. The deformity and muscular abnormality were obvious from birth and in no way altered while the child was under observation in the maternity ward.

The unusual facial lesion made feeding, first by pipette or spoon and later by bottle, difficult and for some time the child's general condition was unsatisfactory.

There was no factor in the maternal history giving indication of possible trauma to the foetus in an early stage of development when myoblastic tissue could be affected. The Wasserman reaction was negative. The parents were unrelated and the older child healthy.

Summary.

A case of amyoplasia congenita is described complicating the later weeks of pregnancy and delivery. Malposition and uterine inertia resulted from hydramnios associated with the foetal deformity.

Recent literature is discussed and the history of the pregnancy reviewed, but no definite indication of the possible cause of the aplasia of muscle is discovered.

I am indebted to Dr. T. Brewis of Scarborough for his kind co-operation as Radiologist and to Mr. V. Watson for the preparation of the photographs. I also wish to express to Sister Waugh of the Borough Maternity Department my thanks for her great care of the child.

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Primary Melanosarcoma of the Vagina
(CASE REPORT)

BY

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PRIMARY sarcoma of the vagina is an unusual malignant neoplasm. It accounts for only 0.23 per cent to 0.61 per cent of all sarcoma of female organs. Melanoma of the vagina is especially rare. A case observed by us is described below.

Existing knowledge concerning melanoma of the vagina has been summarized in the chapter contributed by L. Nuernberger[1] to the Veidt-Stoeckel-Handbuch. This author found 7 cases in the total literature up to 1930 described by Graefe,[2] Parona,[3] Horn,[4] Matthews,[5] Boldt,[6] Eggel,[7] Stefani.[8] Our case, together with that described by Tscherne[9] in 1937, brings the total to nine.

A diagnosis of vaginal melanoma is suggested by presence of a black pigmented tumour in the vagina and is confirmed by biopsy. The condition seems to be most frequent in an age period of 40 to 50. The tumours ulcerate early, give as common symptoms irregular vaginal bleeding associated with sanguino-purulent discharge, show an early tendency to recur and metastasize through blood and lymph vessels, and rapidly involve organs other than the vagina.

In the cases hitherto reported the duration of life after the detection of the tumour was up to 14 months. The prognosis is less favourable than in other growths of the vagina because the value of surgical, radium, or deep X-ray treatment seems to be questionable.

The genesis of the melanic pigment in the cells of vaginal melanoma is still unknown though various theories have been suggested. A striking fact in this connexion is that the pigment is found in tissue of mesodermal origin.

CASE REPORT.

Mrs. B. F., 68 years old, widowed, 6 children, consulted us for the first time on September 22nd, 1940. Menopause at 43, gradual and without special disturbances. There had not been pain or loss of weight. Her family history was essentially negative. Personal history revealed angina pectoris probably of arteriosclerotic origin. Eight months before, she had an apopletic ictus and since then suffered from hemiplegia.

For 4 months she complained of irregular vaginal bleeding accompanied by a malodorus muco-purulent discharge and some sensation of burning after micturition. On examination the patient appeared to be a well-nourished aged woman with evidence of arteriosclerosis, blood-pressure 170/90, heart enlarged, a short murmur over the pulmonary area; the lungs showed a moderate emphysema. In the abdomen no masses or tenderness have been noted. No enlarged lymph glands were found in the inguinal regions. Uterus and adnexa were without pathological changes. Wassermann test, negative. Blood picture, normal. Sedimentation rate, 70.

Chemical examinations of blood and urine, normal. Local examination revealed a large nodular mass involving the anterior wall of the vagina (Fig. 1).

On admission to hospital, the tumour was 4 by 2 cm. in size, rising 2.5 cm. from the vaginal mucosa above the introitus vaginae, with the major diameter in the longitudinal axis of the vagina. The mass adhered to the mucosa and was mobile over the underlying tissue. The tumour was clearly divided into two distinct equal portions: an anterior yellowish and hard portion, and a posterior blue-black, elastic and protruding portion. A biopsy was made on September 22nd, 1940.

The histological examination established the diagnosis of polymorphocellular sarcoma for the anterior part of the tumour and melanosarcoma of vagina for the posterior part.

The patient was then thoroughly examined for metastases. No signs of melanotic tumours were found by ophthalmic examination. X-ray pictures of lungs and bones gave no evidence of metastases in these organs. The urine test for melanin by the method of Solomon and Breen was negative.

It was therefore concluded that the vaginal tumour was a primary melanosarcoma.

Pathological Report.*

(A) Histologically the anterior portion of the tumour (see Fig. 2) was found to contain numerous cells of various forms and dimensions, with large reniform and chromatin rich nuclei. The cells usually had one nucleus, sometimes two and even three. Cytoplasm was generally not abundant, but some cells had abundant protoplasm, and irregular contours. Between the normally-sized cells numerous giant cells were seen. These usually had a clear cytoplasm with irregular borders, sometimes with fine granulations on their periphery and single or multiple nuclei of various forms and sizes. The characteristic structure of striated muscle cells was not evident. Nucleole divisions were found in the various cells observed and were almost always atypical.

(B) The posterior part of the tumour (see Fig. 3) contained cells similar to those observed in the anterior part, but showed greater polymorphism and the presence in the cytoplasm of a brown pigment, in the form of numerous granulations. It was most abundant, filling the entire cytoplasm, and was found also outside the cells. It possessed all the morphological and tinctorial characters of melanin.

Since surgical treatment was contra-indicated because of arterio-sclerotic heart and hemiplegia, combined radium and X-ray therapy was instituted. The patient received 4,000 r on the symphyseal and perineal regions and 980 mg./h. radium in one month (Radium Institute, October 13th to November 15th, 1940). No effect was observed.

For 6 months after the biopsy, the general condition of the patient remained unchanged. Leucorrhoea and sanguinolent discharge disappeared. On the other hand, local examination revealed a new tumour growing out of the posterior wall of the vagina. It had the form and dimensions of a small cherry. Its colour, similar to that of the posterior part of the first tumour, was blue-black. A biopsy was made in March, 1941. Histological examination revealed a polymorphocellular melanotic sarcoma similar to that found 6 months earlier. A second thorough examination of the patient and a urine-test for melanin gave negative findings.

* We are indebted to Professor S. E. Franco and Dr. B. Gelley (Pathological Institute) for their kind help and advice.

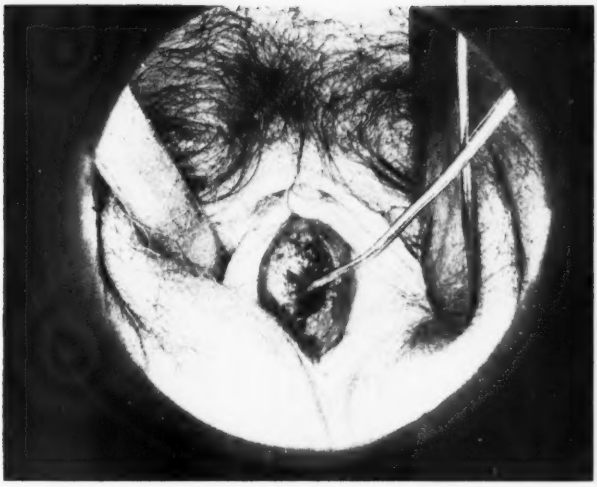

FIG. 1.
Macroscopical view of melanosarcoma of the vagina. The posterior part of the tumour shows black pigmentation.

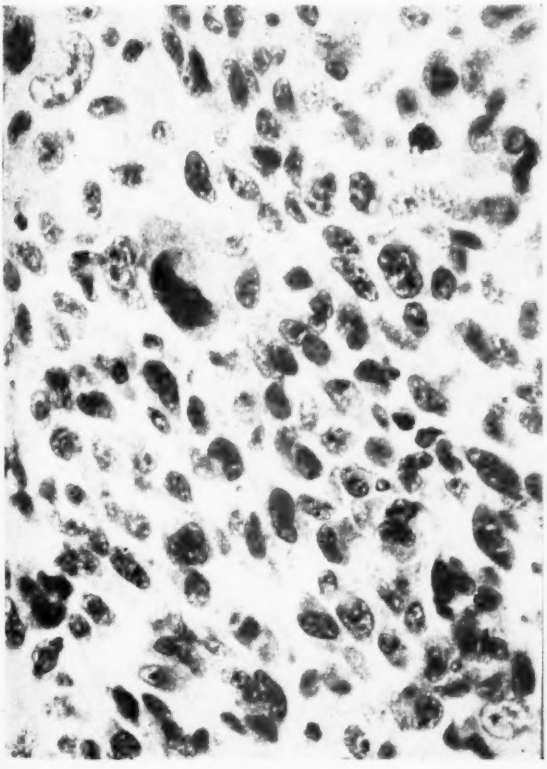

FIG. 2.
Microscopical view of the anterior part of the aforementioned tumour without melanic pigmentation. × 300 enlarged.

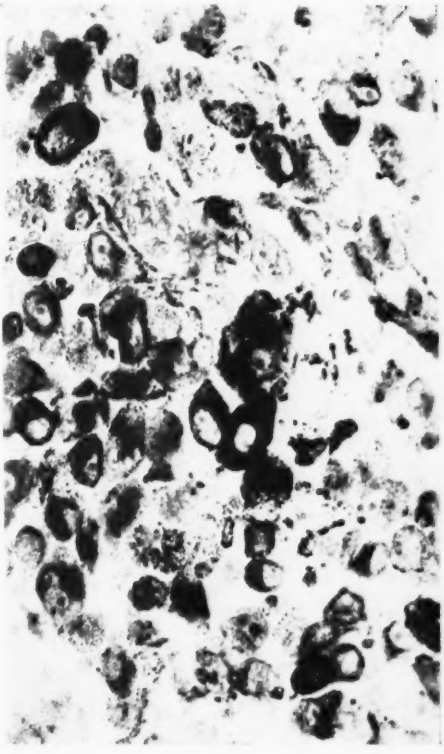

FIG. 3.
Microscopical view of the posterior part of the aforementioned tumour. Note the presence of black pigmentation in the cytoplasm. × 300 enlarged.

MICH.

Metastatic tumours were not found in other parts of the body.

The patient was given a second course of combined X-ray and radium treatment (a total of 1,000 r on the pubic regions and perinaeum and 1,680 mg·/h. radium in the vagina).

The patient was again examined in September, 1941. She complained especially of a most disturbing dysuria and of persisting coughing. The general condition was still satisfactory. No noticeable change was observed in the vagina. The X-ray of the skeleton did not show metastatic growth; that of the lungs revealed numerous metastatic nodules on both sides.

For personal reasons the patient left the hospital. Subsequent clinical developments were reported to us by the attending physician.

In October, 1941, a spontaneous fracture of the humerus indicated the existence of osseous metastases. This diagnosis was confirmed by X-ray. Shortly afterwards the patient contracted bronchopneumonia and died on November 18th, 1941, 18 months after appearance of the first clinical symptoms. Postmortem examination could not be performed.

SUMMARY.

A case of primary melanosarcoma of the vagina (the ninth in the literature) is described. The tumour was located in the anterior part of the vaginal mucosa and metastasized on the posterior wall. Combined X-ray and radium treatment was without effect.

Pulmonary and osseous metastases developed 14 months after the detection of the primary tumour. Death was brought about by bronchopneumonia.

We are greatly indebted to Prof. B. Zondek, head of the department, for his kind advice.

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Self-retraction of Uterus after Portes Operation

BY

HERBERT HOFMANN, M.D.

IN autumn, 1936, the 28-years-old Mrs. L., the wife of a miner, was admitted to the County General Hospital of Most (Czechoslovakia), where I was consultant for obstetrics and gynaecology. The patient was in her second pregnancy and about on term. Her labour had started 48 hours before admission. About the same time the membranes had ruptured and she had strong pains. Prior to admission she had had several vaginal examinations by doctor and midwife.

I knew her and her history very well from the time when I worked on the University Clinic at Prague.

In 1928 she had a stillbirth of about 6 pounds after being several days in labour. She had a flat pelvis with a true conjugate of less than 7½ cm. During the puerperium she developed a vesicovaginal fistula, for the surgical treatment of which she was admitted to the University Clinic and the operation performed by the vaginal route. Unhappily, probably due to the close proximity of the vesicovaginal fistula to the left ureteral orifice the latter was injured and not only did the vesicovaginal fistula not heal but in addition a left ureterovaginal fistula was established. In the postoperative course she developed an infection of the urinary tract, which led to a left pyonephrosis, and some weeks later the left kidney was removed. After the urinary infection had cleared up the vesicovaginal fistula was closed, this time by transperitoneal approach. Altogether the patient was about 12 months in hospital.

When first seen her temperature was 38.7°C. (101.6°F), her pulse-rate 130. blood-pressure 130/95. Urine showed a trace of albumin. Heart and lungs were normal. Her height was only 4 feet 7 inches, and there were definite signs of previous rickets in childhood.

The external examination clearly indicated gross cephalo-pelvic disproportion. The foetus was lying in the left occipito anterior position, the head above the brim and overriding the symphysis. Foetal heart rate 160 to 170, somewhat irregular. Rectal examination showed the cervix fully dilated. Some meconium-stained liquor was discharged from the vagina.

In view of the previous complex history the following facts were to be considered in making a decision as to the method of delivery:

1. The patient was a young woman and childless.
2. She had a flat pelvis of major degree and the vaginal delivery of a living child was impossible.
3. She had previously undergone two operations for a vesico-vaginal fistula and a left nephrectomy.
4. The patient was definitely infected.
5. The foetus was alive but showed signs of distress and it could not be excluded that it had already been seriously damaged.

My conclusions were:

1. Any operation which would include the mobilization of the bladder was out of question.
2. The performance of a classical Caesarean section on this infected case would involve an unreasonably high risk.
3. A craniotomy would endanger the scar of the vesicovaginal fistula.

In these circumstances a Portes Caesarean section seemed to be indicated,

especially as it would give the patient the opportunity of a later pregnancy—important if the foetus should not survive the operation. The latter consideration was decisive in preferring a Portes to a Porro operation.

Under general anaesthesia a lower median laparotomy was performed, the pregnant uterus eventrated, then the peritoneum closed and the parietal peritoneum sutured round the neck of the uterus. Beside this, drapes were placed round the uterus and over the wound. The uterus was opened by longitudinal incision in the middle line, and the child delivered. The male infant of nearly 8 pounds was asphyxiated, but responded to resuscitation. After delivery of the placenta the uterine muscle was closed with two layers of catgut; for the visceral peritoneum of the uterus I used interrupted silk sutures. Uterus and adnexa were then covered with packs soaked with saline and the rest of the abdominal wall closed.

The general condition of mother and child after the operation was satisfactory. Until the end of the 1st week the temperature was elevated to between 101°F. and 102.2°F., pulse-rate 120 to 130; then temperature and pulse returned to normal. All the time saline packs were kept on uterus and adnexa. There was a purulent discharge from most of the silk sutures of the uterus and in the upper angle of the uterine wound an abscess developed and here a uterine fistula was established, apparently by perforation of the abscess into the uterine cavity. The abdominal wound broke down a distance of about 1 to 2 inches.

Due to this complication the second part of the Portes operation, the reintegration, had to be postponed.

Eight weeks after the operation the uterus and adnexa, with the exception of the distal ends of the Fallopian tubes, had practically disappeared under a radiate scar of the abdominal wall.

At this time I had already decided to abandon the second part of the operation and to leave the rest to nature. I limited my further interference to the cutting off of the projecting abdominal ends of the Fallopian tubes.

Ten weeks after the operation the abdominal wound was completely healed, the uterus and adnexa had disappeared and the patient, who by this time was up and about, was fit for discharge.

On bimanual examination the uterus was felt in the abdominal wall; anatomically its position could be compared with that found after extreme ventrofixation.

Six months later the patient had her first menstrual period. On this occasion some drops of blood came from the abdominal scar. Examination revealed that the blood came through a hair fistula which could hardly be recognized with the naked eye.

For 2 years I kept the patient under observation. Her periods were regular, no dysmenorrhoea, and although she was a hard-working woman, she had no complaints. She had become accustomed to the phenomenon of losing some blood through the abdominal scar during her period and refused any suggestion of repairing the fistula. The child was doing well.

Summary.

Although the risk of the Portes operation is nowadays smaller, thanks to the sulphonamide drugs, it is still reserved only for desperate cases, which with improved antenatal and obstetric care are becoming rare.

The above case shows for the first time what happens if for some reason the second phase of the Portes operation is not performed.

A search of various medical indices failed to reveal a similar case.

Obituary

John Shields Fairbairn, B.M., B.Ch., F.R.C.P., F.R.C.S., F.R.C.O.G.

JOHN SHIELDS FAIRBAIRN was born at Bathgate, West Lothian, on December 21st, 1868. He died at his home in Lossiemouth on January 22nd, 1944, where he had had a house, which had been the home of his parents for many years and to which he retired after giving up his active work in London. About 1927 he had his first attack of duodenal disturbance, for which he was under medical treatment for several weeks in St. Thomas's Hospital. After this he had very little trouble for some years but later he had further attacks at intervals, and on several occasions he had to be kept in bed under treatment for several weeks at a time.

He married Elma, the second daughter of J. P. Stewart, of Elgin, who was his much-valued guide and help during his busy life in London, and later, when his health needed her care, she devoted herself to him and had no other thought.

Mrs. Fairbairn, writing to a friend after his death, said John had recently been very well and able to enjoy life, he was only four days ill, became unconscious, and was gone without suffering or weariness. Before the war Fairbairn always spent several weeks each year in London to see his old friends and renew his old associations, but since the very early days of the war the difficulties of travel from Lossiemouth prevented this and in consequence very few of his old friends in London had seen him for over four years. He did, however, write to many and was always most anxious to hear how everybody and everything in which he was particularly interested were standing the disturbances of total war.

His father was the distinguished scholar the Rev. A. M. Fairbairn, D.D., the first principal of Mansfield College, Oxford.

John Fairbairn was at school at Bradford, where at that time his parents were living, and went up to Magdalen College, Oxford, with an Open Science Demyship. In 1891 he took a first class in the honours School of Natural Science. From Oxford he went to St. Thomas's in 1893 and qualified M.R.C.S., L.R.C.P., in 1895 and in the next year took his B.M., B.Ch. (Oxon.).

He was first appointed house physician, then obstetric house physician under Dr. Cullingworth and in 1898 obstetric tutor and registrar. Four years later he became a member of the staff as assistant obstetric physician. In 1900 he took the F.R.C.S., and the M.R.C.P. in 1901. Before he was appointed to the staff of St. Thomas's he was pathologist to the Chelsea Hospital for Women, an appointment that he always felt had been of the greatest value to him in his later work.

From the time he became obstetric tutor at St. Thomas's he was an enthusiastic teacher and keenly interested in education. As years went on his devotion to education and teaching seemed to increase and he became a really great clinical teacher; his interest in the St. Thomas's Medical School and its students never slackened until his retirement.

He always made a great point of the importance of the psychological side of

JOHN SHIELDS FAIRBAIRN

illness and the great influence home difficulties and other anxieties had in aggravating symptoms and preventing the return to health. It was he who first made it clear to most of us that obstetrics was one of the most important departments of preventive medicine.

He was physician to the General Lying-in Hospital and taught midwives with the same keenness as he did the students at St. Thomas's.

He conceived the idea of providing facilities for post-certificate training for midwives to enable them to take refresher courses after being in practice. In connexion with the General Lying-in Hospital he established the Post-Certificate School in Camberwell, which proved most popular and of the greatest value in raising the standard of the work of those who passed through the school. This school has been the model of numerous schools of the kind which have been established in many parts of the country.

The training of medical students in obstetrics was very poor and quite inadequate until recent years. It was due to Fairbairn's foresight and enthusiasm that a complete training in obstetrics for medical students was developed and since then training on the lines he laid down has been adopted by all teaching bodies and is now looked upon as an essential part of a student's clinical education.

He insisted that obstetrics and gynaecology were one and could not be separated and that paediatrics must be part of the teaching of students in a complete training in obstetrics.

At St. Thomas's he fought for, and finally arranged that every student should be appointed for 6 months as a clerk in the obstetric department, during which time he should do nothing but obstetrics, gynaecology and paediatrics. He established at St. Thomas's Hospital the first antenatal and postnatal clinics in London at which students had to attend during their 6 months' appointment.

Fairbairn's work has had a profound effect on the whole outlook on the training of students in obstetrics. Training of students was, in Fairbairn's view, of far greater importance than mere examination results as a guarantee of competence, especially as he felt that many examinations were largely a test of textbook knowledge.

He was a member of the Court of the Society of Apothecaries and was chiefly responsible for the establishment of the Society's Mastership of Midwifery, the first higher diploma in obstetrics ever to be granted. Before a candidate could be admitted to the examination he had to bring evidence that he had had post-graduate training in obstetrics, paediatrics and public health, including a resident house officership in an obstetric unit.

Later, when the College of Obstetricians and Gynaecologists was founded—of which Fairbairn was the second president—similar training requirements were demanded of candidates for entry to its examinations.

Fairbairn was elected F.R.C.P. in 1909, later he served two years on the Council of the College, and in 1934 was Bradshaw lecturer, when he chose as his subject the medical and psychological aspect of gynaecology.

He was made an honorary fellow of the Obstetrical Society of Edinburgh and was given the M.D. of Melbourne and M.M. of the Society of Apothecaries, *honoris causa*.

In his time he held numerous examinerships, including Oxford, Cambridge, London, Glasgow, Birmingham and Leeds Universities, the Conjoint Board and the Society of Apothecaries.

He took his duties as examiner very seriously and had a reputation for fairness and consideration, as many of those who

examined with him had reason to know was well deserved.

He was an early and ardent advocate of a clinical examination in obstetrics and gynaecology and at examiners' meetings to set papers he always tried to get away from textbook questions and to devise those that could be answered properly only by candidates who had been thorough in their ward and out-patient work.

His style in writing was good and lucid and he made numerous notable contributions to the literature of his subject. His textbook "Gynaecology with Obstetrics" was original in many ways, both in form and substance. Its prologue is a valuable contribution to the subject of social welfare in general and gives a clear exposition of the aims of the science and art of obstetrics. He also wrote a thoughtful and clear textbook for midwives.

He was joint editor and author of "Midwifery by the Ten Teachers" and of the "Practitioners' Encyclopaedia of Midwifery and Diseases of Women."

He was a regular attendant at the meetings of the Section of Obstetrics of the Royal Society of Medicine and served as president of the Section. He made many contributions to the Transactions of the society and to various medical publications.

He was at one time Editor of the *Journal of Obstetrics and Gynaecology of the British Empire*, and in this journal he published his important paper on Necrobiosis in Fibromyomata. In 1930 he was inspector in midwifery for the General Medical Council.

In spite of all his administrative and educational activities he was most thorough and conscientious in all his hospital duties, no one at St. Thomas's was more punctilious in the care of his patients and he never spared himself when his services to them were needed. He was an active member of all important hospital committees and was always ready to work hard for developments in any department of the hospital work that he thought to be good.

He was a loyal friend and colleague and I have many reasons for being grateful to him.

Though in retirement, in recent years his wisdom and guidance were of the greatest value to many of us and he will be sorely missed. Fortunately he has left much in his writings that will be an inspiration and help to many who follow.

J. P. HEDLEY

JOHN FAIRBAIRN was above all a man of personality and of character; to these qualities were added great intellectual ability and a wide culture. He was also a man of insight, and this led him to discern, at an early stage of his career, that a wide hiatus existed in the training and competence of obstetric practitioners, for they knew little or nothing of the physiological needs of the infant for whose welfare, during the first few weeks of its life, they undertook the responsibility. Fairbairn accordingly urged with pen and voice that close co-operation with paediatricians should be established in all maternity hospitals and maternity units of general hospitals. Obstetric specialists themselves, in those days, were largely unversed in the technique of such an important matter as breast-feeding and only half convinced that artificial foods were not an equivalent substitute for breast milk. The maternity nurse was usually quite ready to assume responsibility for the baby and she might even regard the intervention of the doctor as unnecessary and unhelpful. Other obstetric teachers took the same view as Fairbairn and a movement of opinion began which gathered such force that to-day the appointment of a paediatrician to the staff

of all maternity hospitals and units is regarded as indispensable.

The antenatal period also attracted much attention from Fairbairn, and it was he who initiated and developed the antenatal organization of St. Thomas's Hospital, which, after that originated in Edinburgh by Ballantyne, was one of the earliest and most successful efforts. It may fairly be claimed for Fairbairn that he was one of the first in London to grasp the importance of the subject and to organize antenatal clinics within the sphere of his own activities.

It may also be recalled that he was one of the original members of the "Preposterous" Club, the semi-humorous title of which was designed to indicate the interest which it took in the mother and child before and after the arrival of the latter. Its members consisted mainly of obstetricians and paediatricians among whom prominent members were Dr. Eric Pritchard and Dr. David Forsyth, who unhappily are no longer with us, Dr. H. C. Cameron, Dame Janet Campbell, Dr. Jewesbury, Dr. Harold Waller and the present writer. The proceedings of the Club were never made public, but the opportunity which it offered for a frank exchange of views was regarded by all its members as of great practical value. It was natural that Fairbairn should take a prominent part in such discussions. His interest in the "expectant mother" was not limited to physical conditions but extended to the difficult problem of her psychological reaction to pregnancy, an interest which culminated later in his well-known Bradshaw Lecture to the Royal College of Physicians in 1931.

He also took great interest in the training of midwives, and was a strong advocate of "refresher" courses for them, which actually were started by him in connexion with York Road Lying-in Hospital.

Fairbairn's nature was genial and friendly and he was a good "mixer." He was a ready and fluent talker, at times a little inclined to prolixity, but his talk was never unduly concerned with his own opinions and achievements. In fact he was one of the least egoistic of men, and never seemed disposed to preen his own intellectual feathers, which he might have done with some justification. He was not particularly interested in games; though he played golf, he was but an indifferent performer and, as is the case with many intellectuals, he looked upon it as a welcome opportunity for conversation. The latter years of his life, disturbed as they were with a good deal of ill-health, were spent in happy retirement at Lossiemouth where his home overlooked the famous golf course.

T. W. EDEN

To appreciate fully the debt which the Central Midwives Board and midwives generally owe to John Fairbairn, it is necessary to refer to the conditions existing at the time of the passing of the first Midwives Act and for some years afterwards. The great majority of the women who had gained admission to the first Midwives Roll were, in a modern sense, untrained, and not a few were quite illiterate. The Board was, therefore, in its earlier years only able to make slow progress in improving the practice of midwives and in securing their better training. When Fairbairn joined the Board the time was ripe for more rapid and definite steps in these directions. The country had been at last aroused on the subject of the welfare of women in childbirth and was requiring for them trained nurse attendants who could take greater responsibilities in their care. Fairbairn never had any doubt of the important part midwives should play in

the midwifery service, and he set himself, with enthusiasm and determination, to secure through the Central Midwives Board that by their training they should be well equipped to play their part. He became the second Chairman of the Central Midwives Board at a time of considerable difficulty when, indeed, the advisability of continuing the Board as a training and examining body was doubted by many. Grave differences had arisen in the general policy to be adopted and disputes with local supervisory authorities were not infrequent. To a large extent the Central Midwives Board had lost the confidence of the country but Fairbairn successfully steered the Board through the dangers which beset it, and left it much more secure and more respected than he found it. Under his guidance the curriculum of training and the methods of examination of the student midwife were entirely revised and a scheme adopted to secure the post-certificate training of all midwives. The outbreak of the war has unfortunately prevented the full functioning of the arrangements which he initiated, but their beneficial effect will ultimately be profound.

Fairbairn was a kindly, considerate, but firm chairman. He was quick to grasp the essential points raised in all debates, and endeavoured to consider every point of view before coming to a decision. He inspired the Board with his high ideals and the members will remember him as a sage counsellor and great leader, whose energetic action in difficult circumstances did much to secure a better midwifery service.

JOHN BUCHAN

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

THE Quarterly Meeting of the Council was held in the College House on Saturday, January 29th, 1944, with the President, Mr. Eardley Holland, in the Chair.

The following candidates were elected to the Membership of the College:

ANTHONY PEARTON BENTALL.

JEAN ROSEMARY BURTON-BROWN.

AGNES ELIZABETH CATHCART.

AUDREY IRENE FREETH.

DAVID FRIEDLANDER.

MATTHEW MACMASTER CARREY.

EILEEN DOROTHY MARY WILSON.

The Council passed a Resolution of sympathy with the British Medical Association on the death of their Secretary, Dr. G. C. Anderson.

The President was appointed to serve *ex officio* as a member of the Committee of Management of the Royal Medical Benevolent Fund.

REPORTS OF SOCIETIES

ROYAL ACADEMY OF MEDICINE IN IRELAND.

A meeting of the Section of Obstetrics was held on Friday evening, January 7th, 1944.

Dr. N. Falkiner, Dr. G. Dockeray and Dr. Cross discussed the

Pathology of Eclampsia.

Dr. L. Cross read a short communication giving the clinical details of three cases of eclampsia as follows:

(1) Patient aged 21, who died undelivered.

(2) Primipara aged 33, severe pre-eclampsia; delivered of twins by the classical section.

(3) Primipara aged 29, severe eclampsia; delivered by lower segment section.

Dr. N. Falkiner discussed the pathology of eclampsia, illustrating the pathological changes by showing microscopic slides of the liver, kidney and placenta in eclamptic cases. He said that certain changes in the kidney, liver and brain were found in postmortem specimens of this condition, which were regarded as being incompatible with life; it was important to discover when these changes actually occurred in the organs. He recommended that every case which died from eclampsia should have a routine postmortem examination performed within a certain time after death, and that the organs should be examined by one or more experienced pathologists.

Dr. G. Dockeray also discussed the pathology of eclampsia, showing specimens of the brain, liver and kidneys. He pointed out that the main pathological features were lesions in the liver and kidneys, and, in cases with cerebral haemorrhage, in the brain. He said that 20 per cent of patients who die of eclampsia show no very marked changes in either liver or kidney; roughly 5 per cent die of left ventricular failure with oedema of the lungs. In a characteristic case of bad liver damage there is a lesion of haemorrhagic necrosis seen on postmortem examination. Kidneys vary; most show marked tubular degeneration.

The President, Dr. A. W. Spain, considered it was a great slur on the obstetricians that they had not yet made any very great progress in finding out the cause of this eclamptic condition. Treatment had improved, but statistics still showed a high mortality rate in the maternity hospitals. He said the microscopic slides were most interesting, especially those of the placenta. He referred to the fact that it was not yet known whether infarcts were the cause or result of the condition of eclampsia. He discussed the treatment and the temptation to do a Caesarean section in certain cases.

Dr. F. T. Geoghegan discussed some of the finer points of the pathology of eclampsia, including fibrinous thrombi in the kidney, liver, brain and retina, and syncytial degeneration.

Dr. T. M. Healy suggested that all the pathological material in the eclamptic cases should be available to the pathologists in the three maternity hospitals. He asked Dr. Falkiner whether he was yet in a position to lay down rules as to operative interference in cases of eclampsia?

Professor W. J. Jessop asked what was the essential lesion in eclampsia? He referred to the pathological changes described by Dr. Geoghegan and asked were they all due to a common disturbance or was one of them a prime factor? He also asked had anyone examined a placenta from an early case of eclampsia and one from a patient who had died from other causes; what pathological disturbances were found?

Dr. Falkiner and Dr. Dockeray replied.

INDEX TO CURRENT LITERATURE

In this Index an endeavour will be made, so far as war conditions permit, to maintain an up-to-date record of all titles bearing on obstetrics and gynaecology and the infant. The classification aims at making immediately available for the reader the titles under the various subject headings. In the majority of instances the title is obtained from the original publication. Where this has been impossible, the title has been obtained from the abstracting journal shown in brackets. Reprints will be welcomed and should be sent to the Editor.

Any inquiries should be addressed to Miss D. F. Atkins, British Postgraduate Medical School, Ducane Road, London, W.12.

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